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Problems Of Drug Dependence 1979

Proceedings of the 41st Annual Scientific Meeting

The Committee on Problems of Drug Dependence, Inc.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Problems of Drug Dependence, 1979

Proceedings of the 41st Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc.

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NIDA Research Monograph 27
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The papers in this monograph were presented or read by title at the 41st Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc., in Philadelphia, on June 4-6, 1979.

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Foreword

The National Institute on Drug Abuse is pleased to publish Problems of Drug Dependence, 1979, in its Research Monograph series. These are the proceedings of the 41st annual scientific meeting of the Committee on Problems of Drug Dependence, Inc., which was held in Philadelphia on June 4-6, 1979.

The Committee, now incorporated as an independent entity, was for 47 years affiliated with the National Academy of Sciences--National Research Council. Its membership is drawn from all fields of clinical medicine, psychiatry, public health, pharmacology, chemistry, and the social sciences. This year, as in previous years, its annual meeting represents a high point in the science activities relevant to drug abuse and neurosciences.

The Committee's annual scientific meetings typically present a truly comprehensive assemblage of reports of ongoing research relating to all aspects of drug abuse and drug dependence. The papers present contributions to new knowledge of agents involved in drug abuse or significantly affecting the central nervous system: their pharmacological action, biological disposition, abuse potential, safety, tolerance liability, or clinical usefulness, and related experimental and clinical methodology.

In addition to papers presented or read by title at the meeting, the proceedings include summaries from a special satellite session on khat and the annual progress reports of NIDA-supported dependence studies of new compounds.

To meet space limitations for this volume, many of the papers have been condensed by the authors. The broad range of subjects treated may be easily seen by looking through the detailed index, which gives full accessibility to the contents.

We believe that this up-to-date review of the field of drug dependence will be of value to readers who will bring to it as wide a variety of backgrounds, interests, and concerns as that represented by the Committee on Problems of Drug Dependence itself.

William Pollin, M.D.
Director
National Institute on Drug Abuse

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at the 41st Annual
CPDD Meeting

Hooked for Thirty Years: Tales of an Investigator

Way, E. L.

It is with deep gratitude and humility that I acknowledge the great honor bestowed upon me today. It is also with considerable pride that I accept the Nathan B. Eddy Award because my peers, rightly or wrongly, have placed me in a niche with such distinguished pioneer investigators as Seevers, Isbell, Wikler, Martin and Kosterlitz, all of whom were or are dear friends.

I first met Nathan Eddy in 1944 and from that time on and until his death in 1973 our paths crossed many times not only at our annual CPDD meetings but also on numerous other occasions. I remember particularly one incident back in the 50's when we were members on an analgetic evaluation committee for the VA. Since we were meeting in San Francisco, I, of course, had to arrive a little late. As soon as I entered the meeting room, Dr. Eddy came up to me and said, "Eddie, I have 60,000 dollars for you," whereupon he reached into his pocket and handed me an ounce of heroin. Since that quantity is equal to about three thousand 10 mgm fixes, at $20 per bag the price would be about right. The integrity of Dr. Eddy was such that he had the complete confidence and trust of the Bureau of Narcotics. As their consultant, he was allowed to push to whomever he wished extraordinary amounts of controlled drugs. To have heroin today, investigators need to have a license registration number and the approval of a joint FDA/NIDA Committee. Although progress appears to dictate the need for more rigid security measures and red tape, I do not know of a single investigator who violated Dr. Eddy's trust.

Before I start discussing some of our investigative work, let me pay tribute to my many colleagues and, in particular, to former students and post-doctoral fellows, with whom I have had the good fortune to have been associated. It will not be possible to name them all but each one has played a significant role to enrich my life by helping me solve problems in opiate research and becoming steadfast loyal friends. Suffice it to say the conditioning I received in their environment is such that if I had a life to live again, my free choice for a career would still be in pharmacology and I would bar press actively for opiates.

My interest in narcotics started with an undergraduate course in pharmacology taught by Chauncey Leake at San Francisco but it was two of my former bosses at George Washington University who "hooked" me. Under George Roth I studied the local anesthetic and cardiac effects of meperidine (known in those days as isonipecaine) but when P.K. Smith succeeded him in 1946 I became interested in drug metabolism. At George Washington together with my first graduate student C.Y. Sung (who will head a pharmacology delegation from the People's Republic of China this coming fall) we found that meperidine was metabolized by the liver to an unknown basic metabolite. Based on these preliminary data I applied for and was awarded a research grant in 1948 from NIH to study the biologic disposition of morphine and its surrogates. I transferred the grant when I moved to San Francisco and with subsequent renewals held it for more than 20 years until I shifted to working on tolerance and dependence mechanisms.

The proximity of San Francisco to Berkeley facilitated the acquisition of N-$^{14}CH_3$ labelled isotopes of meperidine, morphine and codeine and this gave us a running head start over other investigators in this area. N-demethylation was found to be a common metabolic pathway for the surrogates of morphine. In actuality this turned out to be a relatively minor pathway for opiates but it provided a major stimulus for studies on microsomal metabolism. N-demethylation also paved the way for two imaginative hypotheses. Beckett developed a theory of analgesia based on N-demethylation and Axelrod and Cochin postulated N-dealkylation as a mechanism for tolerance. I thought Terry Adler and I had pointedly rejected both hypotheses but I note recently that Fishman et al. have found that N-demethylation of opiates occurs in the brain and as a consequence they have resurrected the early postulates.

I was rather proud of the study on the metabolic fate of meperidine carried out by Nick Plotnikoff as a graduate student because he was able to outline several metabolic pathways without the actual isolation of any of the metabolites and he used a non-specific dye technique for his estimations. By combining the Brodie methyl orange procedure for organic bases with countercurrent distribution, Plotnikoff identified meperidine and normeperidine in the urine by their partition behavior. He then showed that hydrolyzed metabolites of these two substances were biotransformation products by demonstrating that under esterification conditions with ethanol the yields of meperidine and normeperidine in the urine could be substantially increased. Furthermore, evidence that meperidinic acid and normeperidinic acid were also excreted in the urine as conjugated products was indicated by the fact that if he subjected the urine to hydrolytic conditions before esterification, the yield of meperidine and normeperidine could be further enhanced.

Another pathway established for some opiates was O-dealkylation. Terry Adler first demonstrated in 1951 that codeine could be O-demethylated to morphine. To establish this point O-$^{14}CH_3$ labelled morphine was shown to yield $^{14}CO_2$ after parenteral administration

of codeine and morphine was unequivocally identified as a urinary metabolite of codeine by X-ray diffraction studies. Together with Jim Fujimoto, Adler also found that codeine and morphine were N-demethylated to their respective nor derivatives, and norcodeine and normorphine would then be excreted in the urine as conjugates of glucuronic acid.

In those days it was not so simple to demonstrate glucuronide products of opiates because their high water solubility made their purification and isolation from urine by solvent extraction techniques difficult. Oberst at Lexington first demonstrated that the yield of morphine in the urine could be increased substantially by acid hydrolysis but it was not until almost 20 years later that Lauren Woods then at Michigan showed that the "bound" morphine in dog urine was a glucuronide. Shortly thereafter, Fujimoto demonstrated that morphine glucuronide was the chief metabolite of morphine excreted in the urine by humans.

With Sung and Peng we found that methadone is N-demethylated but we had difficulty isolating and identifying the des-methyl metabolites, and it remained for Pohland and associates to demonstrate that following mono- and di- demethylation, the products undergo rearrangement to form cyclic metabolites. In studies on 1-acetylmethadol, Sung and I reported in 1954 that 1-acetylmethadol undergoes extensive biotransformation and that much of its activity results from the formation of an active metabolite. This conjecture has only recently been validated by Mulé, Misra and associates.

Taking a sabbatical leave at Berne with Walther Wilbrandt to study the disposition of heroin, we were able to confirm that heroin was rapidly hydrolyzed to morphine. Later with John Kemp and others we found that the biologic half-life of heroin was less than 3 minutes and that the sequence of hydrolysis involved deacetylation, first to 6-monoacetylmorphine which was then hydrolyzed to morphine. Based on toxicity studies of heroin, 6-monoacetylmorphine and morphine after subcutaneous, intravenous and intracerebral injection, we found that morphine was least potent by the parenteral routes but most potent after intracerebral injection. We concluded from these findings that the primary effects of heroin are due to the formation of morphine. The greater potency of heroin over morphine by the parenteral routes could be explained by the lipid solubility conveyed by the acetyl groups which are than rapidly removed by esterases in the brain. Thus hydrolysis of heroin to morphine in the central nervous system represents an activation process but when it occurs outside the brain in the liver and other organs and tissues, hydrolysis, reflects a detoxification process.

The results of these studies led us to a consideration that the enhanced sensitivity of the newborn to morphine might be attributable to disposition factors. The toxicity of morphine in the rat was studied from birth to one month of age with Kupferberg. The LD50 remained relatively constant for 16 days but between days

16 and 32 it increased abruptly by 4-fold. After developing a sensitive spectrophotofluormetric technique for measurements of brain morphine levels in the newborn, we found that with equal doses of morphine the brain levels in the 16-day-old rat were usually more than twice those in the 32-day-old and in order to attain comparable brain levels with the two age groups it was necessary to administer a dose three times as high in the 32-day-old mice. Thus the results provided an explanation for the difference in toxicity of the two age groups and indicated that the decreased sensitivity to morphine in the maturing animal is due in large part to the development of a blood-brain barrier to morphine. Subsequent studies with heroin and meperidine further revealed that this process was peculiar to morphine. Virtually no CNS barrier development to heroin or meperidine could be demonstrated with increasing age and this was reflected by only small variations in toxicity between different age groups.

With Kaul, Lin, El Mazati, Afifi, Nayak, Berkowitz and others we studied also the disposition of apomorphine, anileridine, noscapine, methotrimeprazine and pentazocine and made generalization concerning the disposition characteristics of basic compounds. Basic drugs are in general more potent than acidic ones because at body pH proportionately more base exists in the unionized form. This property favors their gaining access to target sites for eliciting pharmacologic effects promptly and sequestering in indifferent organs for later release to prolong drug action. By and large, organic bases, including the opiates, have a high apparent volume of distribution because they rapidly leave the blood and concentrate in parenchymatous tissues. Tissue levels can be decreased and excretion facilitated by lowering body pH. These conclusions were summarized and published in a 1962 monograph, Biologic Disposition of Morphine and Its Surrogates, co-authored with Terry Adler.

We took our second sabbatical leave in 1962 and went to Hong Kong to assess the unique modes of inhaling heroin. Addicts there use two techniques: one is by smoking heroin inserted into a cigarette ("ack ack") and the other procedure is by inhaling the fumes resulting from heating a mixture of heroin and barbital ("dragon chasing"). We were informed that dragon chasing was a more effective way of inhaling heroin than ack ack. To find an explanation for this difference, Ben Mo and I decided to compare the urinary excretion of morphine by these two inhalation techniques with that after intravenous administration. Our urinary excretion values of total morphine were consistent with the practice in the field. Based on the percent of the dose that could be accounted for in urine, the efficiency of dragon chasing was found to be two-fifths that of intravenous injection and twice that of ack ack. Under laboratory conditions simulating the two modes of administration, we found that the temperature for volatilizing heroin was critical. At a high temperature such as that of a burning cigarette (746^{o}C), availability of heroin is poor because of extensive decomposition. The addition of barbital to the heroin minimizes the loss of heroin by facilitating the volatilization of heroin at a lower temperature

(244°C). Perhaps, the Hong Kong junkies had a "connection" who was a pharmacist with a sophisticated knowledge of delivery systems!

Although most of our initial work centered on drug disposition studies some of my associates involved me in characterizing sites of opiate action. There is much current interest in the hypothalamic effectsof β-endorphin and these studies relate back to some early work on morphine and hypothalamo-pituitary-adrenal function. Bob George and I reported in the 50's that the hypothalamus is an important intermediary for pituitary-adrenal activation by analgetic agents and that their effects could be blocked by a lesion in the median eminence. Subsequently Bob George and Norio Kokka further noted that growth hormone and gonadotrophin release are also altered by morphine. More recently Eddie Wei (my "friends" identify him as the young good-looking one) found that several mesodiencephalic areas of the brain, the medial thalamic region in particular,are important for mediating opiate antinociception and certain withdrawal signs. Also Edgar Iwamoto has demonstrated that nigrostriatal pathways are much involved in the expression of abstinence.

In 1966 we were invited to attend an International Symposium on Analgetics in Santiago. There I met Professor F. Huidobro and observed his morphine pellet implantation techniques for producing morphine tolerance and physical dependence in mice. In his earlier writing Nathan Eddy has mentioned that tolerance and physical dependence were not characteristic responses in rodents, but as it turns out the earlier workers simply did not administer morphine frequently enough. I was fascinated by the simplicity of the pellet procedure and reflected that I could now study tolerance and physical dependence mechanisms without interfering with my week-end golfing activities.

The pellet made by Professor Huidobro did not quite suit our needs because only limited quantities could be made by a hand press. I consulted Bob Gibson in the School of Pharmacy and he formulated a tablet that could be mass produced and this pellet is now in wide use.

The implantation of this pellet subcutaneously in a mouse for three days produces a high degree of tolerance and physical dependence. A quantitative measure of the degree of tolerance development is given by an increase in the dose of morphine required to produce analgesia and this is generally between 7- and 20-fold. The degree of physical dependence can be quantified by determining the naloxone ED50 to precipitate withdrawal jumping, the greater the dependence the lower the naloxone ED50. Alternatively, Takemori uses the total number of jumps in a group of animals as an index.

Applying these procedures together with some pharmacologic probes we initiated studies in the mechanisms involved in tolerance and physical dependence development. We obtained considerable evidence supporting the biochemical nature of these processes. Like others,

Loh, Shen and I were able to demonstrate the blockade of tolerance development with inhibitors of protein synthesis. We found that cycloheximide not only inhibits the development of tolerance but the development of physical dependence as well. It was also possible to achieve this effect without altering the acute action of morphine and we postulated, therefore, that the macromolecule involved in tolerance and dependence development may be different from the receptor concerned with acute effects and likely was turning over at a more rapid rate.

Inasmuch as the inhibitors of protein synthesis have widespread effects, identifying the macromolecule possibly involved with the development of morphine tolerance and dependence has been a formidable task. Virtually every known putative neurotransmitter has been assessed with respect to its effect on the acute and chronic action of morphine. We (including Shen, Loh, Ho, Bhargava, Friedler, Iwamoto and others) have used various pharmacologic tools to affect as selectively as possible the synthesis storage, release, or degradation of acetylcholine, dopamine, norepinephrine, and serotonin, and the consequences of such maneuvers on the tolerant-dependent state and on the development of tolerance to and dependence on morphine were evaluated.

Based on these experiments, we concluded that acetylcholine, norepinephrine, and dopamine may participate in the mediation of acute pharmacologic responses to morphine as well as certain withdrawal signs in dependent animals but they seem less directly involved with the development of tolerance to and physical dependence on morphine. Although our findings seem to implicate 5-HT to a greater degree, a causal relationship for 5-HT could not be conclusively established, and although our findings have been largely verified by Herz's laboratory they dispute our conclusions. Moreover, Kalant's laboratory note that a selective role for 5-HT in opiate tolerance development can be challenged on the grounds that decreasing serotonin functional activity also reduces alcohol tolerance development and it has been pointed out that a correlation does not appear to exist between brain 5-HT turnover and development of tolerance to other opiates.

There are other pharmacologic tools which can be used to alter tolerance and dependence. Although the same caveat can be applied with respect to interpreting the significance and implication of such maneuvers, it is important to note that the rate of development of tolerance and physical dependence may be reduced or accelerated to varying degrees by pharmacologic agents acting by diverse mechanisms. For example, tolerance can be inhibited by agonist receptor blockade with antagonists such as naloxone or by inhibiting protein synthesis. Although there is evidence less impressive, it appears that reducing serotonin functional activity, β-adrenergic blockade, or reducing γ-aminobutyric acid activity with antagonists such as bicuculline can also reduce tolerance and dependence development. It is of interest to note that tolerance and dependence can be accelerated with agents which oppose the effects of the latter three classes of compounds. Examples are,

respectively: a stimulator of serotonin synthesis (tryptophan), cAMP and its analogs, and inhibitors of GABA transamination. Again, there is no evidence that these manipulations affect directly the causal processes related to tolerance and dependence.

Despite the inability to solve the precise mechanism involved in opiate tolerance and physical dependence, some essential basic information has resulted from the studies. The biochemical nature of the processes was clearly established in that tolerance and physical dependence could be demonstrated to be reduced or accelerated by pharmacologic manipulation. Moreover, the fact that the immediate pharmacologic response to morphine can be modified greatly without significantly altering tolerance and physical dependence development indicates that it is possible to dissociate selectively the process involved in the immediate pharmacologic effects of opiates from those which might be concerned with the development of tolerance and dependence. The converse fact that the development of tolerance and dependence can be blocked without modifying the acute pharmacologic action of morphine also supports this view.

We went back to the drawing board and decided to assess the role of Ca^{++} in opiate analgesia, tolerance and physical dependence. There were compelling reasons that prompted our interests. Takemori first demonstrated in 1962 that morphine inhibits respiration in depolarized brain slices and later Kokka, Elliott and I found that the effect occurred only in the presence of low Ca^{++}. Kaneto reported that Ca^{++} antagonized the analgetic actions of morphine and concluded that opiates may be mediating their effects by altering Ca^{++} flux. Subsequently, Ross found that opiates acutely lowered the Ca^{++} content at nerve endings. In the meantime we had initiated our studies of Ca^{++}-morphine interactions with Harris and confirmed the findings by Kaneto and by Ross. We found that in addition synaptosomal Ca^{++} content increased with tolerance and dependence development. We have since carried out extensive studies on Ca^{++}-opiate interactions.

I should like to present now a personal view concerning the possible mode of action of opiates. Although there are many gaps, the operational model that I am proposing appears to offer a more complete explanation than existing ones with respect to the acute and chronic effects of opiates. Based on the data generated thus far by our laboratory I should like to postulate that the nociceptive state is subject to regulation by the intraneuronal Ca^{++} level. A lowering of the Ca^{++} results in analgesia while elevating Ca^{++} causes hyperalgesia. Thus, morphine and other opiates have been well established to lower neuronal Ca^{++}; however, other agents such as lanthanum, which reduces Ca^{++} uptake, and EGTA, which chelates Ca^{++}, also exhibit antinociceptive activity. On the other hand, the intraventricular injection of Ca^{++} produces hyperalgesia and antagonizes morphine analgesia. Ca^{++} also reduces greatly the agonist effects of normorphine and B-endorphin on the guinea pig ileum. Moreover, the ionophore X537A, which facilitates Ca^{++} entry, augments Ca^{++} antagonism of morphine analgesia, whereas

La^{+++} reverses the antimorphine action of Ca^{++}. These studies were mostly carried out by Harris, Iwamoto, Huidobro-Toro and Hu.

The acute lowering of Ca^{++} by opiates initiates a homeostatic response to prevent Ca^{++} loss. This counteradaptive process requires the presence of morphine and becomes increasingly effective with each successive dose of morphine. Yamamoto, Harris, and Guerrero-Munoz have found that the development of tolerance to morphine is accompanied by an accumulation of synaptosomal Ca^{++} and the subcellular components involved in this increase include the inner synaptic plasma membrane and vesicles. They also found that the increase in synaptosomal Ca^{++} is proportional to the degree of tolerance developed. Since Ca^{++} antagonizes acute morphine action, the accumulated Ca^{++} would oppose opiate effects and more morphine would be required for reducing Ca^{++} to produce analgesia. However, the higher dose of morphine would further enhance the Ca^{++} retention process and render acute lowering of Ca^{++} even more difficult. Thus, a mechanism is provided to explain tolerance.

The proposed cumulative enhancement of Ca^{++} retention by morphine also provides a mechanism to explain cross-tolerance. The elevated Ca^{++} and its increased retention capacity should not only reduce the effects of other opiates but also those of other agents that reduce Ca^{++}. Thus, tolerance to morphine has been demonstrated to result in cross-tolerance to La^{+++} and to EGTA. It could be further argued that since these agents tend to augment opiate effects, they should facilitate the development of opiate tolerance. Consistent with this notion, Schmidt found on comparing the analgetic response to morphine in mice rendered tolerant by morphine pellet implantation and infused either with EGTA or saline that a dose of morphine, which produced analgesia in 50 percent of the saline treated animals, was ineffective in the EGTA group. Conversely, Kaneto and others have reported that repeated Ca^{++} administration inhibits tolerance development.

The development of an enhanced Ca^{++} storage process after sustained morphine administration also offers explanations for physical dependence and the abstinence syndrome. Physical dependence is an invariable accompaniment of tolerance and the two states appear to be closely linked. Under such conditions cytosol Ca^{++} may be maintained at a higher steady state by the enhanced retention process which requires the continual presence of morphine. The need for morphine to support this retention process is indicated by Yamamoto's finding that administration of naloxone to precipitate withdrawal results also in a marked fall in synaptosomal Ca^{++}. Abrupt discontinuance of morphine or antagonist precipitated abstinence results in an increase in cytosol free Ca^{++} at the expense of the retention process and the abstinence syndrome would reflect hyperirritable responses to Ca^{++} that ordinarily are masked by morphine. Hence, when morphine is administered during this state, abstinence would be suppressed because the free Ca^{++} becomes reduced not only by decreased cellular uptake but also by enhanced intraneuronal removal at amplified storage sites. If this be the case, then maneuvers designed to lower free Ca^{++} should suppress

abstinence and elevating it should exacerbate the syndrome. Thus, Harris has shown that La^{+++} decreases the incidence of withdrawal jumping in morphine-dependent mice and increases the dose of naloxone needed to precipitate withdrawal jumping. Conversely, Schmidt has shown that hyperalgesia occurs during abstinence and can be considered to be a withdrawal sign. It is detectable in a dependent animal shortly after discontinuance of morphine and during this state the hyperalgesia can be further enhanced by Ca^{++} administration. Thus, we have qualitative data to support our hypotheses and this provides the framework for validation with more definitive experiments.

Not all of our approaches have been made from the bench. The conceptualization of an operational receptor with molecular models by Cho and Loh has yielded fruitful data beyond expectations. Models of the glycolipids indicate that they might be suitable candidates for binding opiates. In particular cerebroside sulfate yielded excellent correlation between binding affinity and agonist activity. The agreement was obtained not only on the guinea pig ileum with respect to inhibition of electrically induced contractility but also on analgetic potency in mice and humans. To our surprise and delight, the opiate "receptor" isolated from mouse brain by Goldstein's laboratory was found to consist essentially of cerebroside sulfate. Loh's group has persevered in their efforts to validate cerebroside sulfate as an integral part of the opiate receptor and their more recent findings are truly exciting. In collaboration with Bauman's laboratory in Paris, an antibody to cerebroside sulfate has been made which displaces morphine from its central nervous system binding sites and antagonizes its pharmacologic actions. Moreover, the incorporation of cerebroside sulfate by a neuroblastoma cell culture appears to initiate prostaglandin activity in the preparation. Almost certainly there will be increasing activity in the future to assess the role of glycolipids in interaction with drugs.

Thus, our approach towards combating the problems of drug dependence has been essentially pharmacologic and directed towards ferreting the basic mechanisms involved. Although I would without qualification concede that misuse and abuse of chemical substances reflect signs and symptoms of individual and societal maladjustment, I firmly believe that the pharmacologic approach offers, if not the cure, certainly the facilitation that makes psychologic, psychiatric and rehabilitative measures possible. Success with the latter approaches in the past without drug intervention has been notoriously lacking, at least in terms of reaching the major population of addicts.

To a pharmacologist, all drugs are merely chemical substances which ultimately must act on biologic processes. Irrespective of environmental factors, the use of adequate amounts must effect pharmacologic responses by either stimulating or inhibiting cellular activity after their combination at specific sites. It seems reasonable to presume, therefore, that compulsive drug use may be associated with

aberrations in these processes and if this be the case, it should be possible to block or reverse these changes with pharmacologic agents. There are already modest indications that pharmacologic intervention offers good chances for success.

The use of disulfiram for alcohol dependence and methadone for maintenance have not attained universal cures but this should not be expected. Although the successes attained with these agents have been relatively limited, they were achieved with less expenditures of governmental resources in time, effort and money than non-drug approaches. Further studies to dissociate the processes involved with acute opiate effects from those concerned with tolerance and physical dependence offer hope that more effective therapeutic agents can be developed and indeed some are already appearing on the immediate horizon.

In conclusion, I wish to again express my deepest gratitude for honoring me today and for providing me a forum to summarize approximately 30 years of labor described in approximately 300 publications in approximately 30 minutes. I hope that some day ($\leq$ 30 years) I will again be afforded equal time that will reflect more efficient utilization of my efforts.

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The Prescription of Controlled Substances: What's Right and What's Wrong

Cohen, S.

The remark that we live in a drug-oriented society has been repeatedly made. If this is true, it is in part because our citizens have come to expect rapid relief from discomfort, unease and other forms of real or imagined psychophysical distress. Especially, but notexclusively, young people seek chemical solutions for whatever shyness, boredom,or tensions of everyday life they may encounter. Beyond the amelioration of noxious feeling tones, increasing numbers look to drugs to provide them with positive mood states. They search out euphoriants to procure pleasure, ecstatants for joy, and deliriants to deliver them from themselves. Is their demand for pharmacologic surcease a sign of societal decadence, individual failure of nerve, or something else? Whatever it is, the latter day ability to supply chemical configurations that do what is desired with considerable specificity is at hand. And this precision tooling of molecular arrangements inevitably increases demand. It's not better, but easier living through chemistry.

It should be made clear that the physician's contribution to hedonic drug-taking represents only a fraction of the consumer market. The cocaine, heroin, the hallucinogens, the volatile solvents, the cannabis and the array of other psychobotanicals are acquired without benefit of a prescription. Add to these the tobacco and alcohol products, the proprietary medicaments, and we are left with the prescription narcotics, sedatives and stimulants. The supplies of these substances seen on the street are often obtained by theft, highjacking or illegitimate manufacture. Nevertheless, the fraction contributed by the medical profession is important because, for some people, it may initiate or maintain a career of drug dependence, it might cause accidental overdose, or can become a means of suicide.

It was the increased preoccupation with psychochemical consciousness-alteration during the 1960s that provoked the Drug Abuse Prevention and Control Act of 1970. As a result the prescribing of narcotics, sedatives and stimulants became more restricted than previously with criminal penalties available to those convicted of violating the various statutes. Although they make the practise of medicine somewhat more onerous, these controls seem justified. Increasing the pool of abusable drugs simply makes them more readily accessible to users, old and new. The story of the six physicians who

were responsible for the outbreak of heroinism in London has been amply described. We have had similar mini-epidemics in this country. For a while a single doctor was prescribing 2.5 percent of the national supply of methylphenidate. Quick corrective action must be taken against the script doctor or the impaired physician who becomes a supplier of large quantities of mind-altering drugs. A gullible doctor may become overinvolved in writing for narcotics, and then blackmailed into continuing to write. Sometimes, the physician is not even involved -- just his prescription pad.

A second reason for the Drug Control Act was the expectation that patients on dependency-producing drugs would receive closer supervision. No longer could prescriptions for sleeping pills be renewed interminably. This was certainly a worthy goal, and perhaps this hope has been realized in part. Medication supervision is certainly not what it should be at the present time.

There is an ancient German proverb that translated, says: "No soup is ever eaten as hot as it is cooked." Unfortunately, the regulatory broth does not conform to the adage. Certain States have not only adopted the Federal legislation, they have gone far beyond it. They have enacted laws that are considerably more constrictive and their enforcement borders on the inane on occasion. Some states have defined the package insert and the PDR as the basis for medical practise. Deviations from the approved indications or the recommended doses turns out to be illegal, or at least, unethical. For example, the prescribing of a stimulant for an atypical depression unresponsive to conventional therapies can lead to investigations, administrative hearings and a variety of penalties. When the administrative judge, who is not a physician, does not understand the great variability of human responses to psychotherapeutic drugs, things can go very badly for the clinican who tries to do as much as he can for his patient. Unfortunately, judges do not assume responsibility for seriously ill patients.

The prescribing of meperidine for intractable, recurrent, one-sided headaches is probably poor medicine, but what is the alternative by the time the desperate patient has become overtly suicidal. Or consider the case of the busy doctor practising in a poor part of town. A young man (who later turns out to be an undercover investigator) comes in complaining of a running nose, nausea and vomiting, sweating and back pains. A prescription for codeine and aspirin is prescribed after a rather routine history and physical examination. The doctor is charged

with prescribing narcotics for an addict in withdrawal. He had diagnosed a viral infection.

These are actual cases from a single State. I hope that this sort of thing is not the fallout of the Drug Control Act because I confess, I had something to do with its genesis.

So the practise of medicine in some places has become rigidified, frozen in the problematic mold of the package insert. I must remind you that this piece of paper is an agreed upon statement between the FDA and some pharmaceutical firm. I know of no legal stature that it may have involving physicians. Nevertheless, it is being used in courts, not as a guide but as some absolute decree that must not be transgressed. Unfortunately, there are a few patients whose needs do not happen to conform to the arcane pronouncements of the package insert.

Meanwhile, the following situation is taking place, spilling hundreds of dosage units every four minutes onto the black marketplace. A long line of young people extending back over a hundred yards from a doctor's office are awaiting a script for amphetamines or barbiturates or both (slide). It took 14 months to close this operation down.

So what starts out as a laudable effort to deter the diversion of psychochemicals into non-medical channels, culminates as a nit-picking effort to fit the practise of medicine into some committee-constructed Procrustean bed. It may be that those doctors who had the temerity to prescribe amphetamines for an atypical depression, Demerol for migraine-type headache, and codeine for what appeared to be influenza deserved whatever punishment was inflicted. Although they were not particularly contributing to our drug abuse problem, the brand of medicine they practised was not the best. But what of the conscientious doctor who did not want to give a month's supply of sleeping pills or of tricyclic antidepressants to a depressed, indigent person on MediCal or Medicaid? If he wanted to provide such a person with a sublethal amount of these drugs, a one week's supply would be proper. But the rules restrict the number of patients visits, in some instances to one a month. So while the bureaucracy frowns upon what may or may not be poor medicine on one hand, it promotes terrible medicine on the other.

As we look at the changes in the drug schedules since 1970, it is clear that the trend is in the direction of upscheduling. The barbiturate hypnotics have been moved from III to II.

The amphetamines have been similarly treated. Propoxyphene, pentazocine, pemoline, the weight control drugs and the benzodiazepines, previously unscheduled, are now in IV. Methaqualone and phencyclidine jumped from an unscheduled status to II. The only drugs that have gone in the opposite direction are apomorphine and the narcotic antagonists. These changes are probably reasonable in view of the known pharmacology and the recent abuse history of the agents involved.

Specific Drug Classes

1. Stimulants

Cocaine is in Schedule II and retains some occasional usefulness as a topical anesthetic and decongestant. On rare occasions physicians have misprescribed it for its antidepressant or stimulating actions for themselves or for patients. In even rarer instances they provided cocaine prescriptions for profit. The amphetamines, methylphenidate and phenmetrazine are also in Schedule II, and their indications have become more restricted than previously. Narcolepsy and the hyperkinetic behavioral disorders are accepted indications for stimulant use. Their antiobesity effects are in dispute but short courses are permitted. Their use for mild depressive or fatigue states is much more controversial. An occasional patient with an atypical depressive reaction that is intractable to other therapeutic attempts, has benefited from the amphetamines according to a number of clinicians. The amphetamine-related drugs have been the prime agents prescribed by unscrupulous doctors for profit. Weight control substances like fenfluramine (Pondimen) and diethylproprion (Tenuate) are listed in Schedule IV. They have a lesser abuse potential and have rarely been abused in this country.

2. The Hypnosedatives and Anxiolytics

The hypnotic barbiturates and methaqualone (Quaalude) are located in Schedule II. The non-barbiturate sedative-hypnotics are either in III: methylprylon (Noludar) glutethimide (Doriden) and butabarbital (Butisol); or, in IV: phenobarbital, chloral hydrate, paraldehyde, ethchlorvynol (Placidyl) and ethinamate (Valmid). The benzodiazepines and meprobamate also are in IV. These drugs may be overused by patients or diverted into non-medical channels.

3. Narcotics

Opium, morphine, codeine, oxycodone (Percodan),

Pantopon, dihydromorphinone (Dilaudid), methadone and meperidine (Demerol) are all to be found in Schedule II. Codeine combinations with analgesics and paregoric are located in III. Propoxyphene (Darvon) and pentazocine (Talwin) are in IV and the codeine-containing cough mixtures are in V. All of these opioids have been misused by health care professionals or their spouses or diverted to the black market at one time or other. Recently, a large number of Dilaudid tablets was obtained from the UCLA outpatient pharmacy by the forgery of blank triplicate prescriptions.

An organized effort has been underway to reschedule heroin from I to II so that it can be used for severe pain, particularly in the terminally ill cancer patient. In England and Belgium heroin is used for this purpose. Most of it is taken orally. When taken in equivalent oral doses (heroin: morphine = 1:1.5) morphine is at least as effective as heroin according to the studies at St. Christopher's Hospital. Patients given the drugs by the subcutaneous route (usually a 1:3 ratio) cannot distinguish morphine from heroin. When it is given intravenously the somewhat more rapid action of heroin is an advantage. On the other hand, morphine is a bit longer acting. When enormous amounts of a narcotic are needed, heroin has the advantage of greater solubility. Until additional data are acquired, heroin cannot be said to have a distinct medical advantage over morphine, and rescheduling it does not seem to be indicated now.

In addition to what has already been said, a listing of the problem areas encountered in the prescribing of controlled drugs should be mentioned. They include:

1. The diversion of leftover prescription drugs.

2. Patient non-compliance in using amounts of the drugs larger or smaller than ordered.

3. Tolerance development in the insufficiently supervised patient.

4. Poor prescription security such as careless control of prescription pads, pre-signed prescription blanks, erasable prescriptions and improper prescription writing.

5. The failure to do periodic reviews of the drugs the patient is taking.

6. Physician deception by drug-dependent patients.

7. The management of patients with chronic pain or insomnia, and dealing with anxiety in the abstinent addict.

These are all physicians responsibilities. Better education and training are needed to correct poor habits of prescribing and supervising patients on controlled drugs.

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Effects of Scheduling on the Economics of Drug Development

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"Controlled Substances," in the context of the present discussion, refers to those substances covered by the "Comprehensive Drug Abuse Prevention and Control Act of 1970" (Public Law 91-513, 91st Congress, October 27, 1970) and regulations pertinent to the Act beginning with and subsequent to the April 20, 1971 regulations issued by the Federal Bureau of Narcotics and Dangerous Drugs (BNDD) of the U.S. Department of Justice and July, 1971 pertinent regulations of FDA within H.E.W. The BNDD was the predecessor agency to the Drug Enforcement Administration (DEA). The statutory amendment to the Public Health Service Act repealed and replaced the old Harrison Antinarcotic Act and the 1965 Drug Abuse Control Amendments. Essentially, the Act regulates the manufacture, distribution and dispensing of narcotics and/or dangerous drugs through Federal registration of all those involved in this legitimate chain, excepting the ultimate patient user. Research and development activities also are encompassed.

The substances or drugs controlled by the Act are placed in five categories or "Schedules." These are briefly described and illustrated by the following:

Schedule I. This covers certain opiates (including some isomers, derivatives and synthetics) and hallucinogenic substances (such as LSD, marijuana, etc.) for which there is a high abuse potential. These also differ from substances in other Schedules by having no current acceptable medical use in treatment.

Schedule II. Includes certain opiates and opium alkaloids; most narcotics of the former Class A group; stimulants such as straight amphetamine and methamphetamine and some of their combinations, phenmetrazine, methylphenidate, etc. These drugs have a high abuse potential.

Schedule III. Covers depressants, including certain barbiturates; nalorphine; straight paregoric and narcotics of former Class B, etc. These drugs have less potential for abuse than those in II.

Schedule IV. Includes certain depressants such as chloral hydrate, meprobamate, certain long acting barbiturates and such

drugs having a lower potential for abuse than those in Schedule III.

Schedule V. Preparations which contain limited quantities of narcotic drugs and include one or more non-narcotic medicinal ingredients (such as paregoric combination products) for which there is lower potential for abuse than Schedule IV.

Schedule V at present largely relates to some older combination products. Deterrents to the development of new products that might enter Schedule V include the FDA regulatory hurdles to obtaining approval of efficacy claims for combination products, and manufacturing and record controls required for certain ingredients--such as codeine. New combination products of old drugs become new drugs and the difficulties in satisfying regulatory requirements for combinations are likely to make it economically less attractive to develop new products of this class.

Schedule I substances importantly differ from other Scheduled materials in having no current accepted medical use in treatment. The scheduling of pharmacologically active substances in this category also makes it less likely that legitimate medical uses will be sought and developed. Limited access to materials and increased risks and potential liabilities for sponsors and investigators would constrain investigations of such agents in human subjects. There also are ethical problems involved in the use of some of these substances except in very serious conditions.

Schedule I at present may be too broad and heterogeneous a category. Should LSD and marijuana, for example, be in the same Schedule? The first has a much greater known potential for harm, the latter has a much greater incidence of use. Although substances in this Schedule have no current accepted medical use, does such classification virtually foreclose investigations of possible uses of all substances in this class? Should there be subschedules within I so that certain present or future substances within the broad category would be differentiated on such bases as degree of possible harm from infrequent use, ease of access by abusers, and extent of the abuse problem, and the like? At least one substance in Schedule I, tetrahydro-cannabinol from marijuana, is under consideration as a possible therapeutic agent. If a substance in Schedule I were shown to have merit in serious or terminal illnesses, it might be rescheduled in II. However, this would require some sponsor to assume a number of unappealing risks with little potential for reward.

An indirect deterrent of scheduling to the development of new drugs, particularly with Schedule I substances, relates to the constraints on the use of such substances or related materials as chemical components in the synthesis of other possibly useful products. Prototype substances in Schedule I obviously are pharmacologically active. However, constraints associated with compounds categorized by broad Scheduling definitions inhibit the traditional inclinations of medicinal chemists to use these substances as ingredient starting points or even as models for molecular

modifications in the search for new useful medicinal agents. For example, under Scheduled tetrahydro-cannabinols there are included synthetic substances with similar chemical structure and pharmacological activity. Pharmacological activity often appears as a multicomponent profile within which all components are not expressed equally among different compounds of purportedly similar structures. Furthermore, among molecular analogs, homologs or isomers, a chemist often, with equal logic, can relate important points of similarities or dissimilarities among so-called similar compounds, and make equally fallible predictions as to pharmacologically anticipated properties. Class scheduling language that covers as yet unstudied "related" substances can unnecessarily constrain the use of such substances either as starting ingredients or as models in the search for new drugs.

A new drug comes into use through three broad stages--discovery, development and delivery (1,2). Drug discovery encompasses those activities that result in identification of a new drug candidate or new use of a known drug. Drug development covers the range of activities from point of discovery or selection of a new drug candidate that appears to merit clinical evaluation, to release of the product for commercialization. Drug delivery includes manufacture, distribution, purchase, and conveyance of the drug product to the patient. Although science and economics had been the dominant influences on the relationship among these components, in recent years political considerations also have assumed a major role. In examining the economics of any new drug development, the associated economics of discovery and delivery must be concurrently considered before a decision can be reached as to the merits of entering the field to begin with. The impact of Scheduling would become more visible on economics as one moves from discovery through development to delivery. If the economics of delivery are unfavorable, a mission-oriented discovery program would not be justified. An accidental or serendipitous discovery might, of course, change the picture. In any event, the economics of delivery would likely compel a decision as to whether or not to try to develop a product regardless of how the new drug candidate was discovered. With drugs likely to be scheduled, the economics of delivery are just that much more complicated.

The effects of Scheduling should be evaluated not only in terms of current drugs and their categories and the likelihood of similar new drugs falling into the same category, but one also should do some speculating as to how impending regulatory changes and attitudinal trends that may create new regulations might affect the economics of new drug development and delivery. Since the development track is likely to be a long one for a potentially classifiable new drug, the anticipation of changed ground rules and uncertainties surrounding such can serve as a deterrent. There are already so many uncertainties associated with the development of any new drug, that the likelihood of more strigent new regulations or interpretations of existing regulations in the area of Classification of drugs can only be inhibitory to new development.

A substance that is considered as a candidate for entry into a new drug development track and which presently can be anticipated to be subject to Classification should be examined in terms of the kinds of contraints associated with Schedule IV as a minimum and Schedule II as a possibility. Schedule IV drugs require registration, a narcotic permit, additional record keeping, greater security in storage areas, and certain limits on refills; Schedule II additionally demands more stringent record keeping, uses of special order forms, more elaborate security in storage, no refills, and imposes manufacturing quotas. Deterrents to development increase in major quantum leaps as one moves from a non-scheduled to a Schedule IV to a Schedule II drug. The intermediate Schedule III appears closer to IV than to II in its economic impact.

Any new drug having some effect on higher centers of the central nervous system is potentially a candidate for classification. Inhalation anesthetics are not included. Non-drug substances such as volatile solvents (as in some glues) are subject to hazardous abuse by inhalation, but regulation here would be virtually unenforceable. Alcohol and tobacco also are outside the Classification system, but subject to widespread abuse. For that matter, how about coffee and caffeine? Imposed regulations frequently are less related to the magnitude of the target problem than to the social-political acceptance of the regulations.

Any strong analgesic, sedative, hypnotic or stimulant becomes a certain candidate for Classification. It will become increasingly difficult to exclude any centrally acting analgesic from future Classification as such products are likely to fail FDA efficacy requirements unless their effects are substantial, in which event they become almost certain candidates for Classification. Propoxyphene was placed in Schedule IV in 1977, and recently has been the subject of consumer activist pressure to place it in Schedule II. Pentazocine, first marketed some 10 years ago with clinical evidence of relatively low abuse potential, has more recently been subject to abuse and entered into Schedule IV.

The rationale for scheduling becomes further complicated when one considers that abusers of drugs frequently practice polypharmacy. Pentazocine is being taken along with the antihistamine pyribenzamine as a substitute for heroin. Almost any CNS depressant becomes a more dangerous drug when taken with alcohol. Should a drug be Classified as dangerous largely because its abuse is promoted by combination with other substances? In the recent report by the Institute of Medicine entitled, "Sleeping Pills, Insomnia and Medical Practice" (3) it is suggested that control of the availability of drugs should take into account the hazards of combination with other drugs or with alcohol. Secretary of H.E.W. Califano a month ago on May Day told the National Council on Alcoholism that, "We are increasingly concerned about the dangers of alcohol used in combination with certain other drugs" and that H.E.W. "will take major steps to protect the public against the special dangers of combining alcohol with other drugs." He has

asked FDA to compile a list of commonly prescribed drugs that may present health hazards when used with alcohol. This could be quite a list. Further, since public access to alcohol and its consumption is even beyond H.E.W. control, the likely target for further controls are drug products. We may even have a new basis for Classification anticipated on the potential for abuse in combinations.

An impending regulatory change with economic repercussions would derive from sections of the latest (1979) version of a proposed "Drug Regulation Reform Act" originating with Senator Kennedy and his Staff. Senator Kennedy considers the post-marketing surveillance provisions a most important feature of the proposed Bill. Pertinent to the issue of controlled drugs, the Bill proposes that additional scientific investigation also might be required if the drug has known or suspected (emphasis added) risks or is subject to abuse. The drug sponsor would bear the cost. It is generally recognized that we need better means for examination of the performance of certain kinds of drug products in the period immediately following their market introduction--particularly from the perspective of safety. There is a Joint Commission for Prescription Drug Use presently investigating the possible means for improving post-marketing surveillance of new prescription drugs. Post-marketing or so-called Phase IV studies are nothing new for the pharmaceutical industry, and do consume significant resources. This is likely to increase. Greater regulatory formalization of such studies with inclusion of extensive industry surveillance of use by physicians will, of course, add considerably to over-all costs of new drug development and early delivery and particularly so with drugs suspected of an abuse potential. There also can be a self-defeating aspect to highly formalized requirements for post-marketing surveillance. The busy physician will tend to refrain from using a new drug for which he will have to spend additional time with reporting forms or other formalities covering use of the drug--with the result that the incidence of use will be restricted and much more time would be required to gain experience with patient numbers. These several points only illustrate the uncertainties deriving from future changes in regulations which will add to the complexities of development and delivery of new drugs that might be subject to abuse.

Many factors contribute to the economic profile of discovery, development and delivery of any new drug. The likelihood of Scheduling only adds to or complicates this, particularly with such drugs as analgesics, sedatives, tranquilizers, stimulants (antidepressants?), certain antihistamines--or almost any CNS-active drug.

Discovery

Since the mid-1950's, the search for new leads among compounds with possible CNS effects has included screening programs involving a battery of presumptive tests, frequently beginning with

response profiles in the mouse and progressing to more elaborate tests in other animal systems. In more recent years, screening approaches also have involved mechanistically presumptive biochemical tests. Screening methodologies for hypnotic and analgesic propensities go back further in time. Since lab animal model systems usually are developed around responses observed in these animals from drugs with established properties in humans, a limitation of most such laboratory presumptive tests is that they tend to uncover leads to candidate drugs with properties rather similar to those drugs already available. Novel leads among many kinds of drugs have arisen in the course of observing the performance of new drugs in man while using them for some other purpose. This "discovery in man" applies equally to unexpected undesirable as well as desirable properties. Among such undesirable properties have been characteristics leading to abuse. Although animal pharmacological profiles suggesting abuse potentials can be derived from certain drug categories such as opiate related analgesics, other CNS active agents such as minor tranquilizers and moderately potent analgesics have not been as readily assessable. Even more difficult is the prediction of abuse potential for drugs directed to replacement for abuse drugs in the course of treatment. The drug discovery process lacks adequate lab animal model systems for early detection of abuse potential in the laboratory--except among drug categories already established to have distinct abuse potentials. Among these latter, such as strong analgesics, there has been an understandable growing reluctance in the pharmaceutical industry to initiate or continue exploratory new drug discovery programs.

Drug Development to Delivery

If certain programs in drug discovery are inhibited, this obviously will spill over by providing fewer new drug candidates for development. The feed-back relationship also means that the more complicated the development track and less rewarding the delivered result, the less will be the motivation for such mission-oriented discovery programs.

There are considerable differences in development tracks among categories of drugs aside from questions of abuse potential. A new antibiotic, anti-cancer drug, certain diagnostic agents, and the like, can be developed with investment of less time and resources than for example a new anti-inflammatory agent or cardiovascular drug. A new drug to be used infrequently in individual patients, or for use in serious illnesses for which other treatment modalities are of limited value, or for debilitating conditions for which no drug is available--is likely to require a less lengthy development time than a drug requiring chronic administration in a condition for which other drugs are available, or for a drug which perhaps may be considered only to improve quality of life. Drugs with suspected abuse potential, of course, can be expected to have long development tracks.

Certain regulatory trends are likely to further increase the development complexities for all new drugs, and especially CNS-active drugs. The FDA has taken positions implying that we don't need certain new drugs, or don't need them expeditiously, unless they provide a distinct advance in therapy. Although FDA does not have a statutory base enabling it to issue regulations requiring evidence of greater relative efficacy of a new drug in reference to available drugs as a basis for approval of the new drug, there are informal modes for practicing such a philosophy. FDA credits itself--and in a couple of cases with justification--with expediting regulatory approval for marketing of new drugs which it considers to constitute substantial advances in therapy. The other side of the coin is that new drugs which the FDA considers to be minor modifications of existing drugs or to provide little improvement, will languish further in the approval process. Often, the ultimate value of a new drug cannot be assessed until that product has had more widespread evaluation under conditions of practice. Although one might sympathize in principle with the selective expedition of approval of certain drugs, there is little comfort in permitting such a judgment to rest with a government regulatory agency. Certainly, any new drug under a shadow of abuse potential is unlikely to be expedited and would be assured to require a Phase IV surveillance.

As noted earlier in the mention of Class I substances, there are likely to be regulatory constraints--both from FDA and DEA--on new drugs with purported similarity of chemical structure or pharmacological activity with that of an abused drug. Purported similarities and differences usually involve value judgments. Examples abound of chemically similar compounds with markedly different pharmacological properties and dissimilar chemicals with comparable pharmacology. Each substance ideally should be evaluated on its specific properties; however, individual regulatory attitudes on this subject will vary widely and unpredictably.

Laboratory research programs oriented toward some discovery mission may take as little as three years or as long as ten or more years. Although discovery research is highly risky in terms of yield, it is more controllable in terms of resource commitments. Development introduces less controllable economic risks. Perhaps no more than one in ten of new substances launched in a development track becomes a deliverable drug product, and with no assurance of its commercial success. Following discovery, development time in the laboratory may begin from one to two years before submission of an IND and preliminary testing in humans. With a CNS-active drug, or with most drugs involving chronic administration, development activities are likely to occupy eight to twelve or even more years including the period an NDA is pending. Development costs rarely will be less than $1 million per year per drug candidate and be appreciably higher during certain development phases. This excludes the prior costs of research leading to the discovery and research that did not yield drug development candidates.

There are many component activities in a drug development that have increased in terms of unit costs and in elaborateness of implementation. A constructive derivative of the 1962 Drug Amendments was the improvement in the design and implementation of clinical studies and the quality of the resultant data. The time and costs for conducting such studies and processing the results have grown rapidly and continually. Too frequently these have been extended or complicated by conflicting value judgments as to what comprised adequate and well controlled clinical studies, or the statistical interpretation of what might be considered significant, or changes in demands arising from changes in regulations or of regulatory personnel. With certain drugs, such as analgesics, difficulties in clearly establishing efficacy and assessing the potential for habituation, addiction, or other level of abuse, substantially can complicate clinical assessment and materially increase development time and costs. In addition to increases in resources required for support of clinical studies are increased costs of concommitant laboratory safety studies. This of course applies to all new drugs. The so-called Good Laboratory Practices regulations have further increased costs for drug development, with a dubious cost-benefit relationship. Among new drugs with a potential for abuse, further developmental burdens are imposed by DEA regulations governing registration of researchers, security requirements of manufacturers, etc.

Prospective development time and cost estimates for any new drug are made and modified at periodic intervals during a development. This is necessary as the properties of the new drug candidate become better defined and as unforeseen events change the economics of the development. Acceptable development burdens for any new product will vary with time and the perceived needs and opportunities of the development sponsor. Opportunities and costs constitute such a shifting relationship that development cost estimates become subject to frequent changes. A most difficult decision to make and implement is that of terminating a project for economic reasons. Scientists in particular will accept termination of a development if the product appears to be ineffective or has unacceptable adverse effects, but may find it difficult to accept a termination based on anticipated economic deficiencies. With any new drug candidate, major variables contributing to the economics of development include:

a. Unit costs of clinical studies in phases I, II, and III.
b. Investment in material and facilities for preparation of investigational drug supplies (and later for manufacture of the commercial product).
c. Any special laboratory safety studies in addition to usual requirements.
d. Opportunities for introduction of the new product outside the U.S.
e. Time required to develop marketing in the U.S.
f. Probability of competitors' earlier entries with similar products.

For a drug with recognized abuse potential, the first three are likely to require a greater economic commitment and have an overall effect of increasing development time. Increased time results in a compounding of the accumulating economic investment. For example:

a. Costs incurred prior to delivery (drug marketing) become cumulatively compounded in the order of 12% per year and may be higher as costs for money can rise. An investor would be foolish to place money in a development venture in which his past costs are compounded in double digit figures, his chances are appreciable of losing his past investments, and his potential return limited to a short period of time. One could more prudently direct new product development to a field with less risk, or just invest in commercial paper.

b. The return on investment must be adequate during the period the innovator has a sole-source market presence. This usually means during life of the patent. The longer the development time, the shorter the residual patent life. The profitable patent life is further subject to erosion for any drug requiring a Phase IV post-marketing surveillance. Any new drug with a shadow of abuse potential is likely to carry a Phase IV requirement. As abuse potential becomes suspect with more categories of drugs, this Phase IV shadow will lengthen. A post-marketing stricture of three to five years (or more) superimposed on a long development time could consume the patent life of the new drug.

c. The post-patent entry of non-innovative manufacturers would reduce the innovator's income with multi-source competition at about the time the expensive risks already had been assumed by the innovator. Non-innovative manufacturers can enter if it appears the drug is becoming successful, or avoid it if it is not, and have assumed no prior risks in the process. Contributing to this has been FDA's practice of facilitating multi-source entries, largely as a political expediency purportedly in the public interest. With drugs in Class II, there also are manufacturing quotas established by regulation. With a successful Class II drug product, the entry of manufacturers in addition to the innovator would result in a fragmentation of quotas and a further reduction in the innovator's return.

d. Long development time in the U.S. can reduce market penetration abroad. It has become increasingly difficult for American companies to introduce products in some foreign markets prior to obtaining FDA approval for use in the U. S. Regulatory strictures in this country on export of products from the U.S. prior to U.S. NDA approval, and FDA dictation of labeling for products going

overseas further place U.S. companies at a disadvantage in worldwide competition. This can be a greater problem for drugs more likely to be subject to abuse in a U. S. culture than in other countries.

At any one time, an innovative pharmaceutical company will have access to more potential new drug candidates for development than it has reources to develop. This is as it should be and it does require its management to make selections with considerations of the economics of product development and delivery. Placing new categories of drugs in Class IV or escalating Class IV prototypes to Class II, will tend to be an economic disincentive to selection of analagous substances for development. Further, as the strictures of Classification require the assumption of greater economic risks both in development and delivery, there is a further shrinkage in the base of numbers of companies with the resources to assume such risks.

In 1976 and 1977, in the U.S., there was a two-year total of 36 new single drugs, diagnostic agents and biologicals marketed for the first time (4). Of these, new single drugs comprised 7 in 1976 and 8 in 1977. With an industry R. and D. expenditure of the order of $1 billion in each of those years, the U.S. marketed new product output appears small. This reflects on the resources required to bring a new drug or related health product to market, the resources to maintain existing drug products, and expended resources that have not yet or will not yield marketed products.

By the time a new drug is released for marketing in the U.S., that drug product usually will have had several years of use experience in some other countries. That experience helps to anticipate the success or failure of the new drug in the U.S. in terms of medical performance relative to existing drugs and may detect adverse reactions of such incidence that can be observed only from wider use than experiences in development. Successful use abroad, however, is no guarantee of success in the U.S. for a variety of reasons, often hinging on differences in medical practice concepts. Particularly limited may be the value of prior use abroad in assessing the potential for abuse of a new drug. The U.S. appears to have a particularly large, active, and imaginative drug abuse sub-culture. There also appears to be a gray-area of transition of abuse from "legitimate" prescription-inflicted to illegal self-inflicted. This brings about changes in specific drug abuse preferences. In the recent report by the Institute of Medicine(3) the impression is left that benzodiazepines are replacing barbiturates as abuse culprits. With abuse of a new drug, the regulatory solutions usually involve changes in product labeling from FDA and drug Classification by DEA. The economic consequences on the innovative manufacturer can then be quite substantial. If this solves the problem, let the chips fall where they may. Unfortunately, such solutions may be short-lived as the immaginative abuser will turn to something else.

The Institute of Medicine report, for example, acknowledges that controls have reduced the incidence of suicides from barbiturates, but with little effect on the numbers of drug-induced suicides.

Concluding Remarks

During the past twenty years costs of doing business of all kinds have markedly increased. This is particularly true of businesses and industries subject to considerably increased regulations, of which the innovative prescription drug industry is one of the most affected. Present society is far too complex to live without regulations. Regulations, like medicine, should be prescribed within effective dose ranges; over-medication and over-regulation both are dangerous to someone's health. Clinical pharmacology has made more sophisticated the evaluation of optimum dosages of our medicines. We have yet to enter the threshold of objective evaluation of optimum dosages in regulations.

With the human propensity for self-abuse, it is unrealistic to propose that certain drugs with abuse potential not be controlled by regulations. With human ingenuity in discovering new routes to self-abuse, it also should be recognized that there are limits as to how far a government can go in protecting people from themselves. Regulators also can be self-serving and can rationalize the need for more regulations. What would have seemed ludicrous in 1962 as future regulatory extensions of the 1962 New Drug Amendments, in 1979 are regulatory realities. It would be challenging to speculate on the scope of regulations in 1987 based on the Drug Abuse Prevention and Control Act of 1970. The discovery of opioid peptides such as β-endorphin and enkephalins and their possible mediator roles is suggesting an ultimate common or similar receptor route for analgesic effects of as diverse a group of agents as opiates, acupuncture needles and placebos (5). Taking regulatory innovation to logical conclusions, will we see new abuse classifications proposed to cover needles, placebos, and then just as logically, psychiatrists?

In the development of new drugs subject to possible abuse, the burden of classification added to that resulting from new drug regulations in general may become the economic straw that broke the development camel's back. A productive approach at this time could be to resolve regulatory disincentives to the development of new drugs in general and caution prudence in the extension and implementation of regulations governing drug classification. Disincentives derive not only from known regulatory restraints, but perhaps even more so from concern with the uncertainties of threatened further regulations.

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The Impact of Regulations on the Development of Psychoactive Drugs

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Dr. Richard Crout, the capable Director of the Bureau of Drugs of the Food and Drug Administration, said four years ago that regulation must inevitably "cut down on innovation" in the development of new drugs. It is hard to envision a facilitatory role for most regulation. Furthermore, I believe that it is important for people to recognize that regulations are really more important than laws these days. It has been said that we have become a nation governed by men rather than by laws, and I believe there is a great deal in that. This is true for a variety of reasons. To begin with, laws are more general than regulations. Second, one doesn't need to have laws passed in order to have regulations promulgated. Third, regulations can be invoked at many different layers. For instance, one can have regulation at the level of institutional review boards (IRB's). Such IRB's vary considerably in makeup, functioning, and toughness, but they can at times provide major obstacles to research and new drug development, even if only at the level of delaying research. Considerable mischief is possible if an institution decides, in an act of self-flagellation, to appoint "public" representatives of the kind who believe that the only fun in life comes from using dental floss three times a day, jogging, and drinking Perrier water, and who love dogs and cats but hate doctors and research.

Another layer of regulation comes from the Department of Health, Education and Welfare, as exemplified recently by the regulation that information would have to be given when informed consent was being obtained, concerning the availability of compensation for physical injuries suffered by research subjects. There are also regulations that can be promulgated by the Drug Enforcement Administration, or by the states. For instance, my own state of New York is about to repeal the Hatch-Metcalf Act, which in the past has allowed a few dogs and cats to be diverted from pounds to research laboratories. The future consignment of all these animals to the gas chamber will in all likelihood triple the cost of large animal research.

Regulations may also result as the consequence of the deliberations and recommendations of such groups as the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, or the Institute of Medicine.

Finally, and most important in regard to new drug development, the Food and Drug Administration represents an extremely influential source of regulations.

To exemplify the interrelationship between several of these layers, let me discuss some recent happenings as a result of recommendations made by the National Commission for the Protection of Human Subjects and the Food and Drug Administration.

The Commission made a number of recommendations in regard to IRB's. One was that the Department of Health, Education and Welfare should be the single agency for the promulgation of regulations relating to the protection of human research subjects. A second recommendation took up the composition, procedures, authority and facilities of IRB's, in most instances merely describing what is currently the case. Still another recommendation described what should be considered in deciding whether a protocol was acceptable or not, and a final recommendation defined in fairly permissive terms what should constitute a quorum for an IRB to make decisions at a meeting.

The FDA, in turn, came up with recommendations which were much more stringent in regard to the matter of quorum, which asked IRB's to assure the validity or reliability of scientific data, which assigned to the FDA authority to copy records of human subjects, and which limited the ability of IRB's to review and approve the work of any investigator who had participated in the selection of an IRB member for the panel.

As Dr. Robert Levine, a distinguished clinical pharmacologist and member of the National Commission said in an article on this problem:[1] "The FDA has proposed to establish regulations that are contrary to the letter and the intent of the Commission's recommendations. The FDA proposal expects the IRB to perform some functions for which it is incompetent - e.g. assure the validity or reliability of scientific data. It instructs the IRB to collaborate in such dubious activities as facilitating access to patients' medical records. It burdens the IRB with the requirement to perform various tasks of dubious value. And it prescribes heavy penalties for noncompliance with its requirements."

Santayana long ago recommended that we learn from history lest we repeat the errors of the past. What does a survey of the past show?

A lot of unfortunate things have been happening to drug development in recent years, and I believe that many of them can be attributed to excess regulatory zeal. For instance, a short time ago our Center for the Study of Drug Development at the University of Rochester estimated that it took about eight years of human testing and about $54 million to bring a new chemical entity to market. Other estimates have put forth a lower dollar figure, but I believe these are in error because they have not taken into account the considerable amounts of money spent on chemicals that never do make it to market. If one simply looks at the R & D expenditures of American pharmaceutical firms over the years and divides this by the number of new chemical entities brought to

market, I think one will come up with a figure that is close to our estimates.

The most recent data available to us, namely those for the year 1976, show that the total time has now gone up to nine years for the human development phase. About six and a half years of this is the time spent from the filing of the IND to the filing of the NDA, and the rest of the time is spent in processing the NDA. The latter phase has remained fairly static at about two and a half years for some time. It might be argued by the FDA that they are not responsible for the increasing length of time spent in the first phase, but I believe that it is foolish to assert that expectations about what will be required in the NDA phase do not have an impact on how much work is done during the earlier phases. This long duration of gestation obviously means a considerable decrease in the effective patent life for compounds that finally make it to market.

It has also been said that an increased amount of R & D money is spent in nonproductive, so-called "defensive" research, but since I don't have any hard data on that point, I shall say no more about it.

I also sense that in conjunction with this increased duration and expense of drug development, many firms have shown a decreased adventuresomeness in research. This is not unique to the drug industry. It is also being seen at the National Institutes of Health, and in both cases is a reflection of the decreased amount of funds available for research. It used to be said that the NIH peer review system was one of the noblest developments of American science. We used to believe that the system worked beautifully in deciding priorities. In fact, it seemed to work well because there was enough money available to eliminate the need for priorities. Now that the need is there, one finds a good many deficiencies. It is not at all infrequent to hear of study sections turning down research because it looks "chancy", and not predictable in its outcome.

A special side issue is the decreasing likelihood that any company will pursue so-called "orphan drugs", i.e. drugs intended for the treatment of patients with diseases that afflict so few individuals that commercial return will never be adequate enough to pay for their development.

Our data also show a decrease in the rate of new chemical entities being taken into man. For about a decade the number remained static at about fifty per year, but in the last two years of our survey, i.e. 1975 and 1976, this number dropped to about half of the former plateau. The number of IND filings has gone down from a level of forty to fifty per year to about twenty, and it is particularly distressing to note that whereas most of the new chemical entity IND filings by U.S. firms used to be for chemicals originated by these firms themselves, in 1976, for the

first time, more than one third of the filings were for NCEs not originated by these firms.

More and more new chemical entities are being studied abroad for the first time. This number used to be minuscule a decade ago. It has risen gradually to a high of 44% in 1976, and my guess is that it has risen still higher during the years since then.

All these trends might not be so depressing if one could look forward to a counterbalancing of regulatory zeal by external advice. This is unlikely to happen, however, not through any fault of the FDA, but because the current administration has vowed to cut back on advisory committees, and because discussions between HEW and the Justice Department have defined conflict of interest in a manner unlikely to encourage the use of the best advisors.

So much for the past. What about the future? One can foresee developments that are likely to add to the burdens already described. To begin with, there will probably be an increasing interest in developing patient package inserts for drugs prior to their marketing. This will almost certainly delay still further the advent of new chemical entities on the market.

The advent of the so-called "fast track" and "slow track" systems in the FDA poses new problems. First of all, the judgment as to whether a drug is really a major advance is hardest to make at just the point when it is being made -- when it first enters the FDA evaluative system. Second, however, directing the attention of reviewers in the FDA to certain favored drugs will almost certainly mean a slowdown in the evaluation of the chemicals unlucky enough not to be so judged.

There will almost certainly be more post-marketing surveillance studies, which will add to the expense of drug development. I have long argued in favor of post-marketing surveillance, but not of the kind which is currently going on. There are many things about a drug's usage that can only be determined after it is marketed, such as appropriateness of use, degree of misuse, drug abuse, results of gross overdose, etc. What is being measured, however, is primarily the adverse drug reaction performance of a drug, with a view towards checking out suggestions of trouble in the premarketing phase, lest the regulators be embarrassed at the approval of a drug that turns up unpleasant surprises later on in its history. Such studies are extraordinarily expensive and have thus far yielded little of novel interest.

There will certainly be more "gumshoeing" by FDA investigators who, despite the fact that they are not supposed to be engaged in "fishing expeditions", but only examining records where there is good reason to expect fraud, will be in fact looking for whatever they can find unless halted by investigators or institutions. Furthermore, this problem will be compounded by the inclination of certain pharmaceutical firms to ask investigators to sign

general release forms about patients' records, providing even greater authority than is stipulated in the regulations. If a firm takes this attitude, and only awards contracts or grants to investigators who are willing to sign such releases, it will penalize those investigators who quite properly are more concerned about the privacy of patients' records.

Finally, there is the extra obstacle involved in demands by the FDA that a new drug be evaluated for all sorts of indications other than ones of major interest to the manufacturer. It can be argued, quite correctly, that an interesting new anti-inflammatory analgesic will likely be used not only for rheumatoid arthritis but for osteoarthritis, ankylosing spondylitis, and juvenile rheumatoid arthritis even if the drug has only been well worked up for adult rheumatoid arthritis and the manufacturer only wants to promote it for that purpose. Yet, to demand that all of these studies be done before a drug is marketed will mean a delay in access of patients with rheumatoid arthritis to the drug, as well as penalties for the manufacturer, who cannot possibly begin to earn back any money on his investment until all of the studies are done.

What are the roots of all these troubles? One root is stupidity. The FDA is no different from the university world or the industrial world in this regard. There is much more incompetence in this world than there is unadulterated evil, regardless of what romantic people would like to think. I am at least part of the time a university bureaucrat, and honestly believe that my own mistakes are almost invariably the result of stupidity.

But there are also other motivations. There are individuals in regulatory agencies who are ambitious, arrogant, or motivated by a psychotic hate of industrial producers. Some believe that they are better equipped to tell people what is good for them than are people themselves able to judge this on their own behalf. This is depressing to those of us who believe that government should act as an umpire and not as a dictator.

Perhaps most important of all, however, is the absence of any real feeling in the FDA for cost-benefit analyses. It is all too easy for a regulator to promulgate regulations without assessing fully the implications of his moves. If one looks, for example, at the "good laboratory practices" that were prescribed for toxicity testing in animals by, or on behalf of, industrial sponsors, it is clear that the extra work and expense involved in meeting these regulations would spell the doom of any such activities in most universities, since universities do so little of this work that most of them would give up the opportunity to do it rather than shoulder the considerable expense involved in meeting the rather arbitrary requirements.

An especially depressing aspect of bad regulations is that they are very hard to undo. The advice by some that one repeatedly take the government to the legal mat is not really appealing.

It is just not very realistic to engage in litigation every time one runs across a foolish or even dangerous regulation.

More sensible would be an opportunity to have impact on those formulating regulations before the latter are issued for a first view by the general public. Although the preliminary publication of regulations in the Federal Register in theory allows for their change on the basis of comments received by the government such changes are probably harder to achieve than would be the case if the regulations had not yet been published. That is only common sense and human nature.

The government quite correctly would argue back that they cannot show such drafts to a few people because then they would have to show them to everyone. I do not, however, see why our society cannot set up advisory committees of people representing all strata of opinion about regulation who would have a chance to express their opinions on proposed FDA regulations before they were ever published in the Federal Register.

In conclusion, therefore, I believe that our current "drug lag" is attributable to excessive regulation, and that on balance this is not in the interest of the American public, although I would admit that I cannot easily quantify in toto the benefits and the risks that have resulted from this drug lag. I acknowledge that there are others who say that we don't have a drug lag, but a "death lag", and that the public is better off because drugs are so expensive to develop and take so long to reach the market. I am sure that they believe that as devoutly as I am convinced of the opposite.

On the other hand, I believe that the most parsimonious explanation of what has been going on is that the drug lag both exists and is deleterious, that regulation is at the base of the changes, and that a reversal of the present trend would reverse these untoward effects.

It has been said that a pessimist is someone who says that things can't possibly get any worse than they are, and that an optimist is a person who says, "Oh yes they can!".

I am an optimist, but not really that kind of optimist. I agree that things can get worse than they are, but don't believe that they need to get worse. They will, however, never improve unless influential segments of our society demand that they change.

On balance, despite heroin and thalidomide and other untoward results of drug development, the development of psychotropic drugs and of drugs in general have been fantastically beneficial for our society. I see no evidence that we have come to the end of that road unless as a society we insist on putting insuperable obstacles in our own way.

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The Influence of the Mode of Morphine Administration on Tolerance and Dependence

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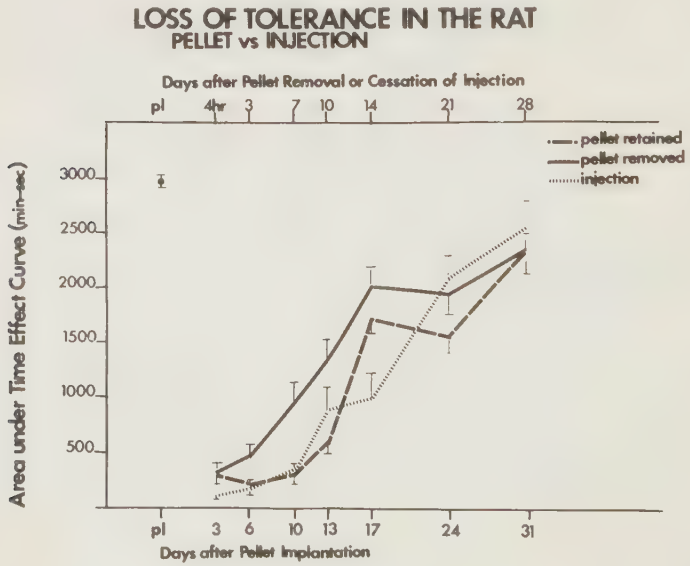
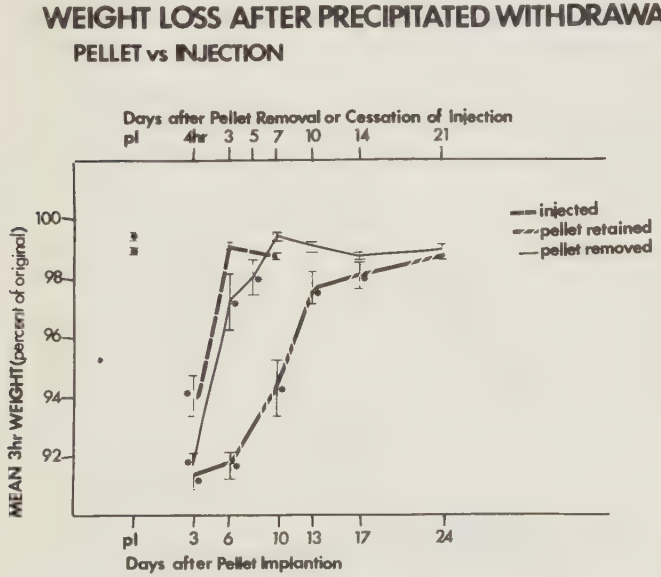
For the past several years, we have, with the support of the Committee on Problems of Drug Dependence, been exploring the effects of implantation of morphine pellets on the development and loss of tolerance and dependence in the rat and comparing this method of drug administration with a series of injections designed so as to approximate the amount of morphine delivered by the pellets. We have also compared the effects of injections and pelleting on both the analgesic and temperature responses in the mouse. Because this is the last report we will make to the Committee about the work that it has supported, we are taking the liberty of summarizing some of the experiments that have been described at previous meetings of the Committee before reporting some new findings obtained in the past year. Figure 1



Analgesic response to a single injection of 15 mg/kg MS at the days indicated on the abcissa.

(Cochin et al, 1978a) shows the comparison of the effects of a series of injections, pellet-retention and pellet-removal on tolerance to the analgesic hot-plate response in the rat as elicited by the injection of a 15 mg/kg test dose of morphine sulfate at the indicated intervals. Although the degree of tolerance after three days of injections or after three days of pellet in situ is maximal, this tolerance disappears significantly more rapidly in the group of animals in which the pellets were removed than in the groups of animals that received injection or in which the pellets were retained. However, four weeks after pellet removal or termination of injections, the degree of tolerance is identical for all three groups, although even that long after pellet removal or termination of injection the animals are still slightly tolerant. We believe, therefore, that although there are quantitative differences in the rate of recovery of drug sensitivity, probably related to the amount of drug released by the pellets over time, pellet implantation is not qualitatively different from other forms of drug administration.

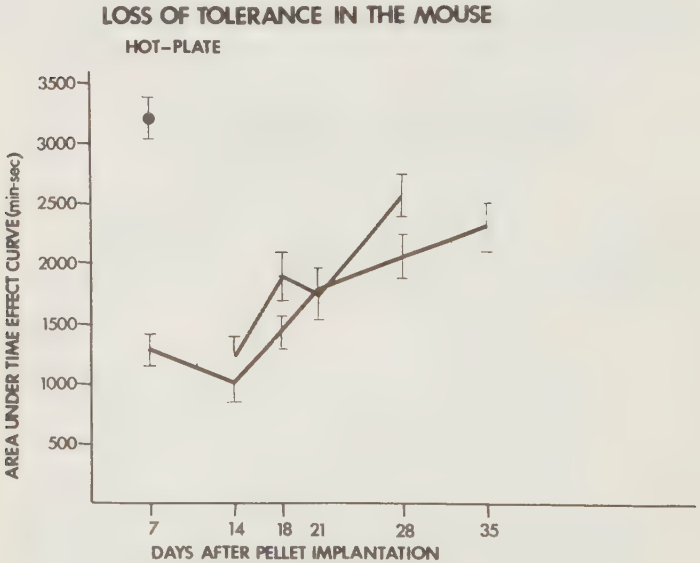
We also investigated the onset and disappearance of physical dependence using the three-hour weight loss after naloxone-precipitated withdrawal as an index of the presence of and severity of physical dependence. Although we observed other signs of physical dependence such as ptosis, wet-dog shakes, jumping, diarrhea and tooth chattering, we found weight loss to be the most easily quantifiable and very sensitive as well. Figure 2



Onset and disappearance of physical dependence in the rat as measured by 3-hour weight loss after a naloxone (10 mg/kg) challenge given at the indicated times.
** = P < 05 compared to placebo-pelleted group.*

summarizes the results obtained in those experiments. Three days after the beginning of treatment, all groups of animals were profoundly dependent on morphine, but the injected group (broken line) demonstrated less physical dependence than the two pelleted groups and lost that dependence more rapidly. By three days after the termination of the injections, there was no significant weight loss after naloxone challenge in the injected group. This rapid loss of dependence is probably caused by the patterns of drug administration and the levels of drug administered during the three days of injections. The group of animals from which the pellets had been removed three days after implantation also showed rapid loss of dependence, significant weight loss no longer being detectable a week after the pellets had been removed (solid line). The group of animals in which the pellets were allowed to remain (slashed line) showed a much slower return to control values with significant weight loss observed for at least 12 days longer than the group in which the pellets had been removed.

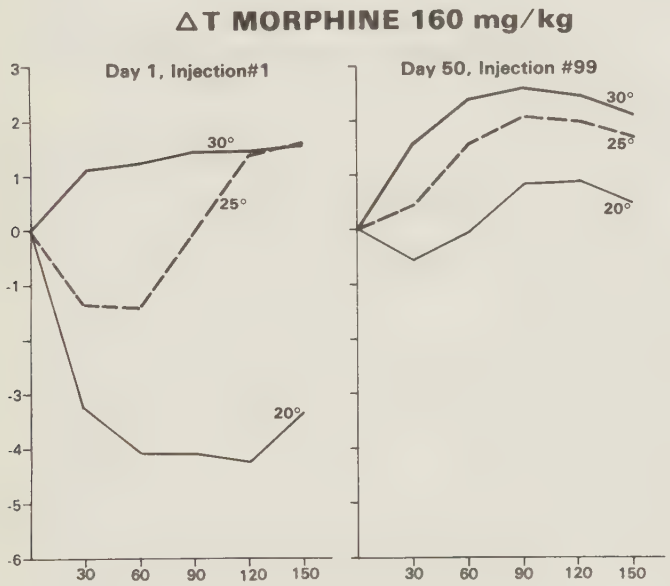
We also compared the development and loss of tolerance in the mouse with respect to analgesia as measured by the hot-plate assay and by morphine-induced temperature changes. Earlier work in our laboratory has shown that it is difficult to induce tolerance in mice to the analgesic effects of morphine by giving multiple daily injections. Pelleting has made the demonstration of the development of tolerance in this species much easier. Figure 3 shows that mice pelleted with a single 75 mg morphine



Loss of tolerance to the analgesic effect of morphine sulfate (20 mg/kg) in morphine-pelleted mice. Solid line: single group of mice tested repeatedly. Broken line: data for separate groups of mice, each group tested on only one of the indicated days.

pellet will show a significant degree of tolerance for as long as 35 days after pellet implantation and that animals tested repeatedly with a 20 mg/kg morphine injection (solid line) showed a greater degree of tolerance than those that were tested only once. However, even the pelleted animals that were given only one morphine injection (broken line) showed residual tolerance 28 days after pellet implantation (Cochin et al, 1978a). We still have to look more systematically at the degree of residual tolerance with respect to analgesia in animals in which pellets are removed after three days. Attempts to show residual tolerance after a single morphine injection in an unpelleted mouse have not been successful thus far.

The effect of morphine on body temperature in the mouse is an assay system which we have used very extensively in our laboratory and which we have described at several previous meetings. It is possible to show tolerance to the hypothermic effect of morphine after a series of injections or after morphine pelleting (Miller et al., 1977, 1978; Cochin et al.,1978b). Figure 4 shows

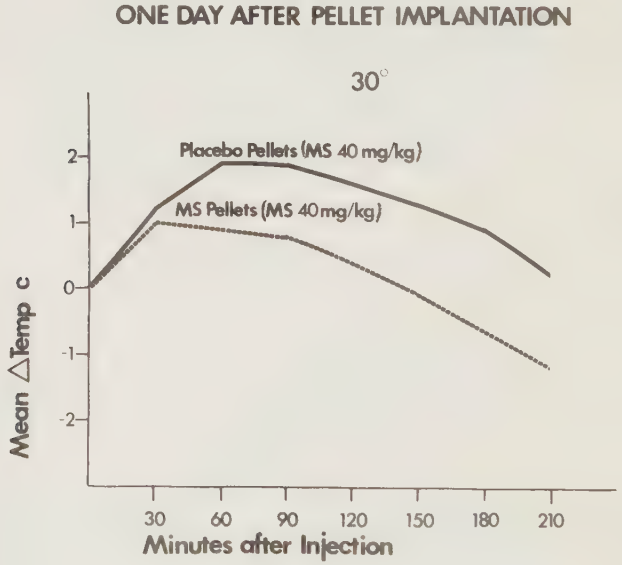


Temperature response of mice to 160 mg/kg of morphine at three ambient temperatures.

the effects of twice-daily injections of 160 mg/kg of morphine for 50 days at three different ambient temperatures. As can be seen, the hypothermic effect almost disappears at 20 degrees and is converted to hyperthermia at 25 and 30 degrees. In pelleted mice, one can see a more striking reversal of the hypothermic

effect and indications of the loss of tolerance a month after pelleting. The temperature effect can also be used to measure cross-tolerance either after injections or pelleting.

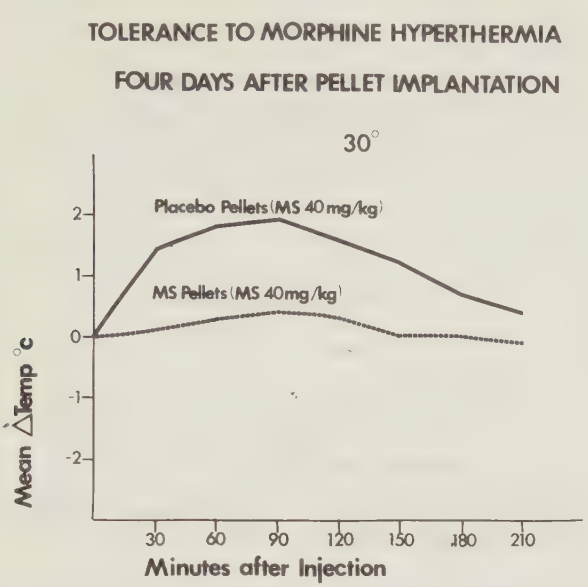
The studies described above concern themselves with tolerance to the hypothermic effect of the opioids and opiates. In the past year we have turned to a study of tolerance to the hyperthermic effect of morphine. It has long been believed that no tolerance developed to the hyperthermic effect of morphine and one sees many references to this in the literature. We have not understood this because even if hyperthermia is a stimulatory effect some tolerance should develop to it and it should be reversible by the antagonists. At this time we will address ourselves only to the first point, that of the development of tolerance. Since we were never able to see any indication of tolerance development to hyperthermia in mice that received 160 mg/kg of morphine twice a day for 50 days, we decided to pursue this further by using morphine-pelleted animals rather than injected animals (Miller et al., 1979). Groups of mice were implanted with either morphine or placebo pellets and were then tested at various intervals after implantation. Figure 5 shows



Tolerance to the hyperthermic effect of morphine (40 mg/kg) in mice one day after pellet implantation.

the results obtained one day after the implantation of a 75-mg morphine base pellet and after a test dose of 40 mg/kg of morphine was administered. It is evident that there is a significant decrease in morphine hyperthermia at 30° ambient temperature although there is still a discernible effect. Four days

after pellet implantation an injection of a 40 mg/kg test dose demonstrates almost complete tolerance to the hyperthermic effect (Figure 6). We do not believe that these results are

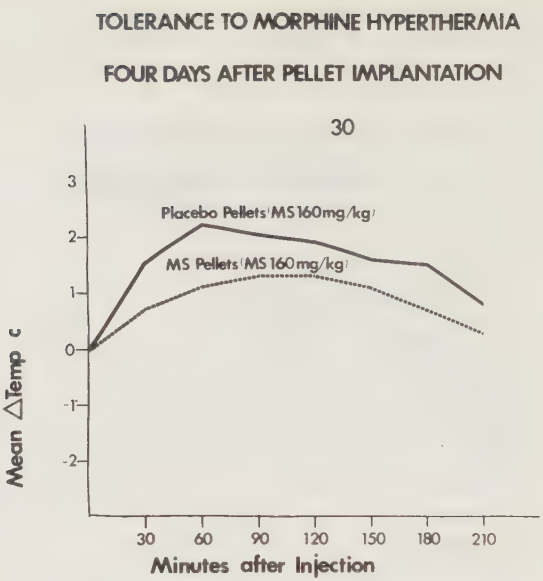


Tolerance to the hyperthermic effect of an injection of morphine (40 mg/kg) in mice four days after pellet implantation.

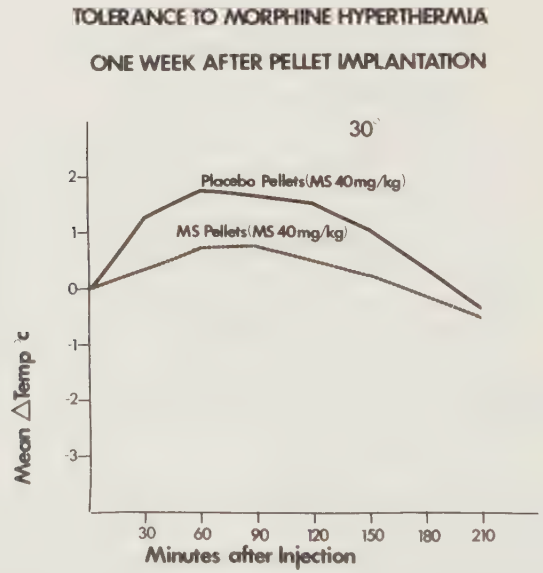
different than those seen after a water or saline injection.

It is, of course, a well known fact that tolerance is a function of dose as well as time. Figure 7 shows the results obtained in animals implanted four days previously after receiving a dose of 160 mg/kg of morphine rather than 40 mg/kg and it is obvious that there is incomplete although measurable tolerance to the larger dose. The difference between the placebo-pelleted and the morphine-pelleted mice is much smaller than that in the groups given 40 mg/kg. Figure 8 shows a return of drug sensitivity in morphine-pelleted animals that received a 40 mg/kg test dose one week after pellet implantation. One still sees an attentuated response but it is nowhere near as marked as the response to the same test dose observed in animals four days after pellet implantation (Figure 6).

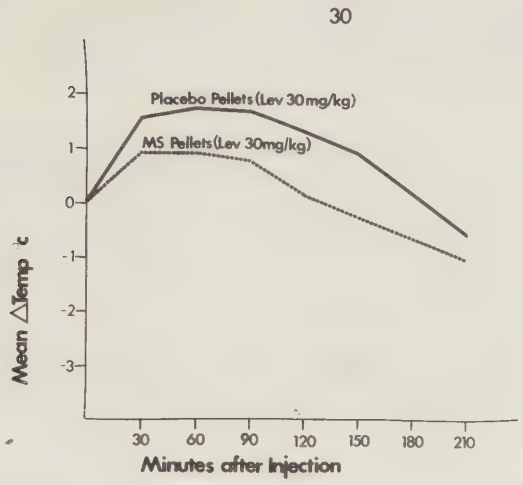
This assay system can also be used to study cross tolerance to opiates other than that in the implant. When mice implanted with either morphine pellets or placebo pellets for one week are given 30 mg/kg of levorphanol there is significant attenuation of levorphanol hyperthermia in the morphine-pelleted group (Figure 9). The difference between the two levorphanol curves is almost as great as is the difference between the two



Tolerance to the hyperthermic effect of morphine (160 mg/kg) in mice four days after pellet implantation.



Tolerance to the hyperthermic effect of morphine (40 mg/kg) one week after pellet implantation.



Cross tolerance to the hyperthermic effect of levorphanol (30 mg/kg) in mice one week after morphine pellet implantation.

morphine curves a week after implantation (Figure 8). This is not surprising since 30 mg/kg of levorphanol is approximately the equivalent of 40 mg/kg of morphine in this assay system.

The differences between the two curves can also be measured precisely as shown in Table 1 which lists the areas under the curves in minute-degrees for the experiments shown in figures 5-9.

It is apparent that both hypo- and hyperthermia are excellent assays for tolerance and cross tolerance and that one can get a more quantitative estimate of the degree of tolerance by measuring the differences in response between two groups of animals. We have also demonstrated that hyperthermia is an opiate effect to which tolerance develops and some preliminary experiments in our laboratory also demonstrated that hyperthermia can be blocked by naloxone (Miller et al., 1979).

Finally, we would like to describe experiments using a technique developed in E. Leong Way's laboratory. We had been having some problems in removing the pellets because they were either heavily encapsulated or were in a form whose outline was very difficult to define. Dr. William Schmidt, a student of Dr. Way's, told us about a technique in which pellets were wrapped in small nylon bags cut from a larger piece of pantyhose. Although the exact brand of pantyhose is not important,

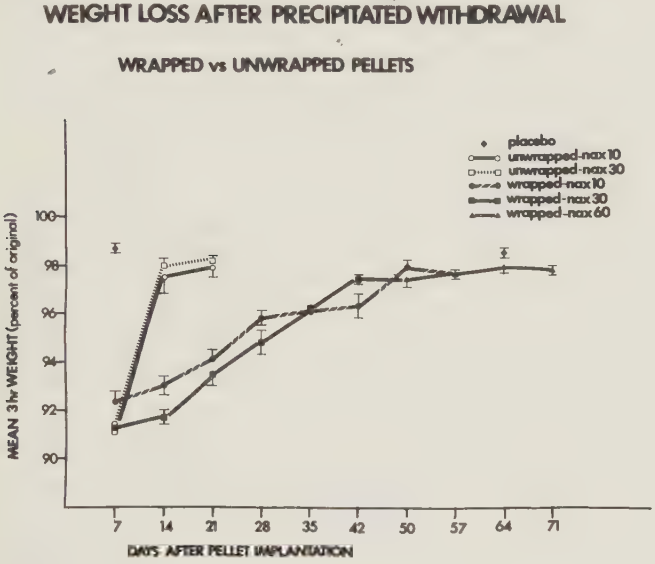
Table 1

THE USE OF AREA UNDER CURVE OF HYPERTHERMIC EFFECT TO MEASURE TOLERANCE AND CROSS TOLERANCE IN MICE

Drug Dose (in mg/kg)	Pretreatment	Area After Drug Injection (min/degrees)
	One Day After Pellet Implantation	
MS 40	Placebo Pellets	128.85
	MS Pellets	75.75
	Four Days After Pellet Implantation	
MS 40	Placebo Pellets	140.85
	MS Pellets	18.25
MS 40	Placebo Pellets	175.95
	MS Pellets	95.40
	One Week After Pellet Implantation	
MS 40	Placebo Pellets	120.70
	MS Pellets	47.57
Levorphanol 30	Placebo Pellets	121.70
	MS Pellets	70.70

the mesh probably is. We used the upper part of the garment which is made up of heavier material than is the stocking part. We proceeded to wrap a number of pellets and then repeated that part of our earlier experiments in which the pellet was allowed to remain in the rat. To our surprise, we were able to detect significant dependence as measured by 3-hour weight loss after naloxone challenge for 52 days after the implantation of a wrapped pellet. It took 59 days for the animals to become indistinguishable from controls. This contrasted with the results with implantation of unwrapped pellets after which it took only 17 days to return to control values (Figure 2). We then decided to undertake a new series of experiments which would compare in a systematic fashion the delivery of morphine via unwrapped pellets or via nylon-enshrouded pellets, using the disappearance of dependence as the measure of drug effect.

The animals used in these experiments were adult male Wistar-Lewis rats weighing 250 to 300 grams. All were housed in general animal quarters with food and water freely available. Three groups of animals were used. One group was implanted with two 75-mg morphine-base wrapped pellets, another with two 75-mg morphine-base unwrapped pellets, the third group was implanted with two placebo pellets. The animals were tested for dependence at weekly intervals from 7-71 days after implantation of the pellets. Half the animals in each of the pelleted groups were given a challenging dose of 10 mg/kg of naloxone to precipitate abstinence, the other half received 30 mg/kg. On day 50 the group that had received 30 mg/kg of naloxone was given a dose of 60 mg/kg and on day 57 and thereafter all rats received a dose of 60 mg/kg of naloxone. The results are shown in Figure 10. The open squares and circles represent the



Three-hour weight loss after naloxone challenge in rats implanted with morphine pellets either unwrapped or nylon-wrapped. The naloxone challenge dose (in mg/kg) is indicated in the key.

unwrapped pellets, the closed circles, squares and triangles the wrapped pellets. As can be seen, rats with the unwrapped pellets return to control values within 14 to 21 days after implantation, while the animals with the wrapped pellets showed significant weight loss as compared to the controls through day 50 with both 10 and 30 mg/kg of naloxone, and on day 64 after a 60 mg/kg naloxone dose (triangle). Except for the first two test days there is no difference between the effects of 10

and 30 mg/kg naloxone challenge doses. One can speculate that had we given 60 mg/kg instead of 30 all the way along, the difference between these two lines in the graph would have been exaggerated, but this is something that would have to be shown experimentally.

With respect to signs of physical dependence other than three-hour weight loss our results are as follows: In the animals in which the pellets were not encased, the only signs seen two weeks after pellet implantation were diarrhea and ptosis and by three weeks after implantation, diarrhea and ptosis were seen in only 20% of all the experimental animals regardless of the challenging dose of naloxone. In the animals which were implanted with nylon-wrapped pellets, however, the results were quite different. Nine out of 17 animals demonstrated jumping behavior 42 days after implantation, and this behavior was seen in a small number of animals for as long as 71 days. A significant number (6 out of 17) had diarrhea on day 64, not severe enough to result in weight loss after the 42nd day, but present, nevertheless. Ptosis was also observed in 4 out of 17 animals 64 days after pellet implantation. Wet-dog shakes were not remarkable except for the first week and we do not believe that they constitute a very sensitive indication of the presence or absence of physical dependence.

It is clear that encasing the pellet in a nylon mesh bag is a way of ensuring that there is steady release of small amounts of morphine throughout a period of several weeks. It is also clear that this is an inexpensive and stable delivery system which depends on passive diffusion at a rather constant rate for its effectiveness. If the tie of the bag in which we put the pellet is, for some reason or another, forced open, then the results resemble those seen with unwrapped pellets. Several animals in the wrapped-pellet group gave results that were similar to those observed in rats in which unwrapped pellets were implanted and recovery of the nylon bag showed that much of the morphine base had already been extruded and that the walling off of the pellet was like that which would be seen with the unwrapped pellet. It is obvious then that the bag serves to protect the morphine pellet as much as it serves as a vehicle to deliver the morphine to the animal.

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Biosynthesis of the Enkephalins in the Myenteric Plexus of the Guinea Pig Ileum: Further Analysis of the Interaction of the Enkephalins and Their Analogues With the Opiate Receptors

Kosterlitz, H. W.; McKnight, A. T.; Corbett, A. D.; Gillan, M. G. C.; Paterson, S. J.; Robson, L. E.; and Sosa, R. P.

In this paper, we are reporting on the research of the Unit for Research on Addictive Drugs during the past year. The results which were obtained have been submitted for publication elsewhere in more detailed form.

BINDING SITES OF VARIOUS OPIATES AND OPIOID PEPTIDES IN HOMOGENATES OF GUINEA-PIG BRAIN[1]

The binding of a number of tritiated agonists to opiate receptors was studied in homogenates of guinea-pig brain by a modification of the method of Pert and Snyder (1973). The compounds could be divided into a group with low numbers and another group with high numbers of binding sites (Gillan, Kosterlitz and Paterson, 1979a; Gillan, Paterson and Kosterlitz, 1979b). To the first group belonged ligands which in an earlier investigation (Kosterlitz et al., 1979) had been assigned to interact preferentially with δ-receptors, e.g. {^{3}H}-D-Ala^2-D-Leu^5-enkephalin or the μ-receptors, e.g. {^{3}H}-dihydromorphine. Their maximal number of binding sites were 7.4 ± 0.3 pmol/g brain tissue (n = 5) and 4.26 ± 0.36 pmol/g brain tissue (n = 4), respectively. On the other hand, the number of binding sites of {^{3}H}-D-Ala^2-L-Leu^5-enkephalin amide (n = 5) were 12.4 ± 0.9 pmol/g and of {^{3}H}-etorphine 15.4 ± 2.5 pmol/g (n = 3). It may be concluded that the latter two ligands combine with both the δ- and μ-binding sites. When cold ligands were tested against their respective labelled ligands, it was found that for the displacement of {^{3}H}-D-Ala^2-D-Leu^5-enkephalin 84 times more cold morphine was required than for the displacement of {^{3}H}-dihydromorphine. On the other hand, for the displacement of {^{3}H}-dihydromorphine only 3.7 times more cold D-Ala^2-D-Leu^5-enkephalin was required than for the displacement of {^{3}H}-D-Ala^2-D-Leu^5-enkephalin. Thus, considerable cross reactivity was found for D-Ala^2-D-Leu^5-enkephalin. D-Ala^2-L-Leu^5-enkephalin amide, which has similar affinities to both receptors, was equally effective in displacing {^{3}H}-dihydromorphine and {^{3}H}-D-Ala^2-D-Leu^5-enkephalin.

SPECIFIC PROTECTION OF THE BINDING SITES OF D-ALA^2-D-LEU^5-ENKEPHALIN (δ-RECEPTORS) AND DIHYDROMORPHINE (μ-RECEPTORS)

Although there is now considerable evidence in favour of the existence of more than one receptor with which the opioid peptides interact (Lord et al., 1977; Gillan et al., 1979a,b; Kosterlitz et al., 1979), it was thought desirable to obtain a more direct proof by examining whether or not appropriate ligands specifically protect the binding sites against inactivation by alkylating agents (Robson and Kosterlitz, 1979). Phenoxybenzamine was chosen as an alkylating agent because it has been shown that it inhibits the specific binding of {^{3}H}-naloxone irreversibly (Cicero, Wilcox and Meyer, 1974; Spiehler, Fairhurst and Randall, 1978). It was found that, in homogenates incubated at 37°C for 15 min, phenoxybenzamine inactivated μ- and δ-receptors to the same extent, the IC_{50} values varying between 0.8 and 1.3 nM. To obtain an inactivation of 70-80%, a concentration of 2.4 μM of phenoxybenzamine was required. The principles of the experimental procedure in the protection experiments were based on preincubation with varying concentrations of the cold ligands for 10 min at 37°C whose protecting power was to be investigated before the homogenates were exposed to the action of phenoxybenzamine for 15 min at 37°C. The cold ligands were removed from the homogenates by centrifuging, reconstituting the homogenate from the pellet and incubating it for 15 min at 37°C. This procedure was repeated once before testing the achieved protection by binding assays with either {^{3}H}-dihydromorphine or {^{3}H}-D-Ala^2-D-Leu^5-enkephalin (40 min, 25°C). The results showed that the binding of {^{3}H}-dihydromorphine was protected about 6 times better by cold dihydromorphine than by cold D-Ala^2-D-Leu^5-enkephalin and that the binding of {^{3}H}-D-Ala^2-D-Leu^5-enkephalin was protected about 20 times better by cold D-Ala^2-D-Leu^5-enkephalin than by cold dihydromorphine. No such selectivity was found when D-Ala^2-L-Leu^5-enkephalin amide was used for the protection of either the μ- or the δ-binding sites. The results of these experiments constitute so far the best evidence for the existence of μ- and δ-binding sites because the cross-over design excludes metabolic effects.

ENKEPHALIN PRECURSORS IN THE MYENTERIC PLEXUS OF GUINEA-PIG ILEUM[1]

It has been shown previously that, in the myenteric plexus of the guinea-pig ileum, the enkephalins originate from unknown precursors produced locally by ribosomal synthesis (Sosa et al., 1977; McKnight et al., 1978). It has further been found (Lewis et al., 1978) that, in the striatum of various species, peptides of 40,000-100,000 daltons occur and, on tryptic digestion, yield fragments that bind to the opiate receptors of brain homogenates. It has been suggested that these peptides may be precursors in the biosynthesis of enkephalins.

Analogous putative precursors have now been isolated from the myenteric plexus of the guinea-pig ileum (McKnight et al., 1979). Preparations were homogenised in 5 volumes of 10% (v/v) acetic

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acid containing 0.01% (w/v) dithiothreitol and centrifuged at 49,000 g for 30 min. The supernatants were applied to 1.5 x 50 cm columns of Sephadex G75 and eluted in the same solution used for extraction but containing 0.02% (w/v) sodium azide. In the early experiments, 2 ml fractions were collected, dried and re-dissolved in 200 µl of Krebs solution without bicarbonate. Generally, a 100 µl aliquot was taken with 100 µl of a 1 mg/ml solution of trypsin treated with diphenyl carbamyl chloride (Sigma) in 0.1 M Tris hydrochloride (pH 7.8 at 37°C) for incubation at 37°C. The remaining 100 µl was used for a control incubation without trypsin. Digestions were terminated by acidifying to pH 2 with HCl. The digested and non-digested samples were transferred to 10 x 0.5 cm columns of Amberlite XAD-2 with 0.1 M HCl. After washing with distilled water the columns were eluted with methanol. The eluates were evaporated and the dried samples were dissolved in the modified Krebs solution for bioassay on the mouse vas deferens.

When the effects of electrical stimulation were examined, control and stimulated (10 Hz) preparations were incubated for 2.5 h in Krebs solution containing a mixture of amino acids (1 µg/ml) (Sosa et al. 1977). When synthesis of proteins and enkephalins was to be inhibited, the Krebs solution of both the unstimulated and stimulated preparation contained cycloheximide (0.1 mM). In these experiments, 8 ml fractions of eluate from G75 columns were collected, freeze dried and dissolved in 1 ml modified Krebs solution and digested with 400 µg of trypsin in 1 ml 0.1 M Tris. After a 2 h digestion the samples were purified and assayed as before. In certain cases, the active fractions after digestion were purified by thin layer chromatography.

The elution patterns of materials causing a naloxone-reversible depression of the contractions of the mouse vas deferens showed one area of activity in the total volume and another area which eluted generally between 30 and 60 ml from the G75 column, which corresponded to material of a higher molecular weight of between 10,000 and 20,000 daltons. No activity was ever observed which corresponded to material larger than 20,000 daltons even after tryptic digestion for 16 h. The total activities of the high and low molecular weight materials after digestion were approximately 100 and 200 ng methionine-enkephalin equivalents per gram of tissue, respectively; in control samples incubated without trypsin only the activity due to the low molecular weight material was found. Since this was unchanged by tryptic digestion, it was assumed that the low molecular weight material probably consisted of enkephalins.

The possibility that the active products after tryptic digestion of the high molecular weight material might be enkephalin-like was supported by pharmacological tests using both the vas deferens and the myenteric plexus assay tissues. The active fractions were more potent in the former tissue in producing naloxone-reversible inhibitions, confirming that the activity was "enkeph-

alin-like" rather than "β-endorphin-like" (Waterfield et al., 1977).

The proposal that the crude extract of the 10,000-20,000 daltons material might include peptides which were the precursors of the enkephalins was tested by examining the effects of electrical stimulation and cycloheximide on the levels of the putative precursors. Control tissues had a mean content of naloxone-reversible activity after tryptic digestion of the high molecular weight peptide of 140 ± 27 ng/g (n = 3). Stimulation alone or cycloheximide alone did not significantly alter this value. When tissues were stimulated in the presence of cycloheximide the content of enkephalins was reduced by about 70% ($P < 0.005$). Although the exposure of myenteric plexus preparations to cycloheximide reduced the incorporation of {^{3}H}-Tyr into proteins by 93% after only 1 h, the mean content of the naloxone-reversible activity after tryptic digestion in preparations stimulated for 2 h in the presence of cycloheximide was not significantly different from the unstimulated control value.

Preliminary attempts to identify the active products of tryptic digestion of the 10,000-20,000 daltons material were performed by thin-layer chromatography of pooled active fractions. In each of four experiments, unstimulated or stimulated, in the absence or presence of cycloheximide, the activity patterns were similar. Activity was present at the origin and in the band preceding the band due to standard methionine-enkephalin, which itself contained only little active material, but no activity was found in other areas of the plate. No activity corresponding to leucine-enkephalin was detected.

The results from our experiments on the effects of stimulation and cycloheximide may be taken as evidence against the view that all of the "enkephalin-like activity" generated by tryptic digestion can be related to original precursor molecules. After stimulation in the presence of cycloheximide, the total enkephalin content of the myenteric plexus preparation fell. Since previous work had shown that this depleting effect was maximal after this time (Hughes, Kosterlitz and Sosa, 1978; McKnight et al., 1978) we might have expected to see at least a similar reduction in the level of the putative precursors. Since this was not the case, it would appear that not all the large peptides yielding on tryptic digestion fragments interacting with opiate receptors are precursors of the enkephalins. It has been shown that the incorporation of {^{3}H}-tyrosine into proteins of preparations of myenteric plexus is virtually abolished by 0.1 mM cycloheximide (Sosa et al., 1977) but whether any residual capability of the cell for protein synthesis might exist and whether this might be able to maintain sufficient stores of precursor is not known.

The possibility that cycloheximide may inhibit the enzymes responsible for conversion of precursor to enkephalin or prevent their synthesis must also be considered.

ACKNOWLEDGEMENTS

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FOOTNOTE

1. The sections on Binding Sites of Various Opiates and Opioid Peptides in Homogenates of Guinea-Pig Brain and on Enkephalin Precursors in the Myenteric Plexus of Guinea-Pig Ileum appear in somewhat modified form in Endogenous and Exogenous Opiate Agonists and Antagonists, E. Leong Way, editor, copyright 1980, Pergamon Press, Inc., Elmsford, New York. They are used with permission of Pergamon Press and may not be further reproduced without their specific permission.

The Binding of LAAM and Its Metabolites to Blood Constituents

Toro-Goyco, E.; Martin, B. R.; Harris, L. S.

INTRODUCTION

A diversity of reports indicate that *in vivo* the narcotic analgesic LAAM[1], which shows an opiate-like profile (Fraser and Isbell 1952) is converted to two major metabolites, namely α-acetylnormethadol (McMahon, Calp, and Marshal 1965) and α-acetyldinormethadol (Billings et al. 1973). Both metabolites have been found to remain in the circulation for prolonged periods (Billings, McMahon, and Blake 1974) and there is existing evidence that a significant portion of the activity of LAAM is due to its metabolites (Billings et al. 1973; Nickander, Booher, and Miles 1974). LAAM and its metabolites have been found to bind to the opiate receptors of rat brain (Horng, Smits, and Wong 1976).

Despite the fact that the binding of drugs to plasma proteins is well established as an important parameter in the pharmacological and therapeutic activities of medicinal agents, no studies, to our knowledge, have been reported on the binding and distribution of LAAM and its major metabolites to blood constituents.

In this work, we report the distribution of LAAM between RBC and plasma proteins. By using the techniques of gel filtration and equilibrium dialysis, we studied *in vitro* the nature, extent and reversibility of the binding of LAAM and its metabolites to plasma proteins. We also identified a LAAM binding fraction in plasma and characterized it as a high molecular weight α-globulin present in low (about 1 mg/ml) concentration.

MATERIALS AND METHODS

Drugs: LAAM, tritiated in carbon 2 of the heptyl chain, specific activity 38.06 mCi/mmole, (Batch No. 1634-88); nor-LAAM, tritiated in the o,o' carbon atoms of the phenyl rings, specific activity

[1]Abbreviations used: LAAM, (-)ℓ-α-acetylmethadol; nor-LAAM, (-)α-acetyl-N-normethadol; dinor-LAAM, (-)α-acetyl-N,N-dinormethadol; $CsCl$, cesium chloride; SDS, sodium dodecyl sulfate.

1.40 Ci/mmole (Batch No. 2014-148-2); dinor-LAAM, tritiated in the o,o' carbon atoms of the phenyl rings, specific activity 94 mCi/mmole, (Batch No. 2150-2) and methadone, tritiated in the o,o' carbon atoms of the phenyl ring, specific activity 16.7 Ci/mmole, (Batch No. 1709-148B-8) were obtained as their hydrochloride salts from Research Triangle Institute (Research Triangle Park, N.C.) as authorized by the National Institute on Drug Abuse. All the compounds were over 95% purity as determined by radioscan after chromatography. The above named unlabelled compounds were also supplied in crystalline form by the same organization.

Chemicals: Optical grade ultrapure C_sCl was from Nutritional Biochemicals. All other chemicals were CP or reagent grade.

Materials: Sephadex G-200, 40-120 μ, 30-40 ml bed volume/gm dry gel was obtained from Pharmacia.

We used Glenco gravity flow columns 1.5 x 100 cm, 1.5 x 60 cm, and 5.0 x 100 cm for gel filtration chromatography. Experiments were done at a room temperature of 20 + 3°C. Absorbancies were detected with a IsCOUA-5 absorbance monitor and recorder (Instrumentation Specialties Co., Lincoln, Nebraska). The eluent was collected in tubes in an automatic fraction collector. Radioactivity was counted in a Beckman liquid scintillation counter. Quench was corrected, whenever necessary, by external standardization. Blood was collected into evacuated blood collection tubes (vacutainers) from non-fasting, apparently healthy individuals with no current or past history of narcotic abuse. When sera was desired, blood was collected in the absence of anticoagulants, allowed to clot at room temperature and centrifuged immediately thereafter. The sera was removed and stored at 4°C. For larger amounts of plasma, outdated blood from the institution's Blood Bank was used.

The time course of binding of the different drugs to serum proteins was determined by dialysis. Equilibrium dialysis was used to determine percent binding of drugs to protein. Bound/free ratios were calculated at various concentrations of drug for Scatchard's plots (Scatchard 1949).

The basic apparatus for the dialysis has been described before (Judis 1976). The dialysis tubing was prepared by heating for 1 hr at 80° in the presence of 1% EDTA and soaking in water with 0.1% EDTA until used. Dialysis was carried out at 20° ± 3°. The electrophoretic mobility of the LAAM-binding fraction was determined by Sepraphore polyacetate electrophoresis and estimation of its molecular weight by SDS gel electrophoresis. Gels were prepared as suggested by Maizel (1966) and molecular weights were estimated as suggested by Weber and Osborn (1969). Proteins of known molecular weights (Sigma Chemical) were used as standards in the calibration curve for molecular weight determination. Quantitative protein determinations were made by Sutherland's (Sutherland et al. 1949) modification of the Folin reaction. Spectrophotometric measurements were done in a Model 635 Varian UV Vis spectrophotometer.

RESULTS

Distribution of LAAM in blood constituents. The results presented indicate that in whole blood, LAAM is nearly evenly distributed between RBC's and plasma proteins. The results were consistent for the six subjects studied. It must be emphasized, however, that the subjects used for this study had not been recently exposed, to our knowledge, to LAAM or any other opiate-like drugs and significant differences could occur in individuals exposed to LAAM or analogous drugs. Evidence of the weak nature of the binding of LAAM to plasma protein was obtained by Sephadex G-200 gel filtration. The elution pattern indicated that even when the serum proteins were allowed to equilibrate for 18-24 hr with this drug, almost all the drug, as shown by the radioactivity used to trace its presence, was eluted after the proteins. The radioactivity coincided with the elution of other small molecules present in plasma which absorb at 280 nm and that elute with the total volume (or volume accessible for diffusion) of the chromatographic columns. This chromatographic behavior is in marked contrast to highly lipophilic drugs such as the cannabinoids, that are strongly bound to plasma proteins and elute from the column together with the proteins[1]. Since the metabolites of LAAM (nor-LAAM and dinor-LAAM) have been found to last periods of over 48 hr in plasma, we also performed a gel chromatographic study of these drugs after equilibration with plasma to ascertain whether their chromatographic behavior was different and might be a clue for their long lasting presence in plasma. Their elution behavior did not differ from that of LAAM.

Equilibrium dialysis. Our experimental approach to equilibrium dialysis was to allow the plasma proteins to accumulate the drug until saturation. The time taken to attain saturation was determined by removal of aliquots from the dialysis bag (and dialysing buffer) at various time intervals until the ratio of bound/free drug reached a plateau. This plateau was attained 24 hr after start of the dialysis. Bound/free ratios were calculated from samples removed at 36 hr or longer.

Reversibility of the binding of LAAM. Our data indicates that the binding of LAAM was readily reversible. When the drug was incubated with plasma, and the ratio of labelled:unlabelled drug was 1:5, serum proteins bound a significant higher amount of radioactivity than when lower ratios (1:25 and 1:50) were used. After the addition of a 10-fold excess of unlabelled drug, thus decreasing the labelled to unlabelled ratio from 1:5 to 1:50, the amount of radioactivity bound per ml of protein diminished reaching the same values of radioactivity bound when the dialysis was started with a labelled to unlabelled ratio 1:50. An identical effect was observed when LAAM (labelled:unlabelled ratio 1:5) was incubated with serum protein and the ratios were decreased 1:25 and 1:50 by the addition of unlabelled nor-LAAM and dinor-LAAM. It can be inferred from these results that the binding of LAAM is highly reversible and that the

[1]B. R. Martin and E. Toro-Goyco - unpublished data.

metabolites compete for the same binding sites. The reversal of the situation, the displacement by LAAM of one of its metabolites (dinor-LAAM) and the opiate methadone from their binding sites was studied also. After 24 hr equilibration of serum with the drugs, addition of an excess of unlabelled LAAM (50 x) caused their displacement from the binding sites as shown by a decrease in the amount of bound radioactivity per ml plasma.

The results of our equilibrium dialysis experiments show that the binding affinity for LAAM and its major metabolites nor-LAAM and dinor-LAAM, and methadone is of the same order of magnitude when their respective concentrations in plasma are identical (1 nmole/ml or 1 μM). We also found that for any particular one of the above drugs in serum at the concentrations used, a 5- to 10-fold excess of any other of the drugs studied causes a displacement of the binding of the same order of magnitude. These results are also consistent with the fact that binding is weak and reversible and that the four drugs studied here compete for the same binding sites.

Identification of the LAAM binding fraction. Our failure to isolate and identify a serum-protein-LAAM complex by gel filtration led us to simulate conditions that favor an equilibrium between drug and protein. Equilibration of a chromatographic column with a buffer containing a given concentration of drug (in this case LAAM) favors the presence of a LAAM-protein complex no matter how weak it may be. This is true for any ligand provided appropriate concentrations of the ligand are found in the eluting buffer. This approach enabled us to identify a specific plasma fraction with affinity for LAAM. This fraction eluted between the first and second protein peak of the chromatogram. Neither the immunoglobulins nor albumin showed any appreciable binding of LAAM.

Further characterization of the LAAM binding fraction. Further characterization of the LAAM binding protein indicates that it has the electrophoretic mobility of an α-globulin. On SDS gel electrophoresis, because of dissociation of polypeptide chains in the several proteins comprising this fraction, several different bands of varying molecular weights were observed. However, two of the sharpest bands in the gel correspond to particles of molecular weights close to 400,000.

A Scatchard plot traced to determine specific binding indicate that one ml of plasma binds close to 3 nmoles of LAAM. These results corroborate the data which indicates that albumin plays an insignificant role in the binding of LAAM and suggests that the drug must be bound by a protein of low concentration in plasma.

DISCUSSION

Several factors determine the rate at which a drug leaves the circulation. Among these are the drug's partition coefficient, or ratio of solubility in lipid to solubility in water, molecular weight and state of aggregation in plasma. For drugs like LAAM and its metabolites, which are of low molecular weight and water soluble, these

factors alone would favor their rapid disappearance from plasma. The remaining factor, state of aggregation, is very important in determining their long lasting presence. Our results show that at drug levels found in humans treated with these drugs (100-1000 ng/ml serum) (Billings, McMahon, and Blake 1974; Kaiko and Inturrisi 1975), the fractional binding and the partition coefficient could be important parameters in determining their continuous presence in plasma. In the absence of a renal active process for the clearance of the drug from plasma, only glomerular filtration will account for their removal in urine. If the fractional binding is high, as shown by our results, the amount of drug available for glomerular filtration rate is significantly diminished. Despite a high fractional binding, strength of binding is weak. This last factor favors rapid removal from plasma. Unfortunately, there is no information available as to what the fate of LAAM and its metabolites is after glomerular filtration. The indirect evidence at hand (long duration in spite of weak plasma binding) suggest that reentry of the drug into the circulation by reabsorbtion cannot be discarded as a possibility.

It has been reported (Toffaletti, Savory, and Gittelman 1977) that in subjects receiving LAAM, 24 hr plasma levels show the simultaneous presence of LAAM and its two major metabolites, but the bulk consist of the metabolites. Our results suggest that this may be accounted for by the displacement of LAAM from its binding sites by its metabolites. Probably the higher lipid:water partition ratio of LAAM[1] contributes to its removal from plasma in preference to its metabolites.

We must conclude that the evidence presented here cannot support a statement asserting that the long lasting presence of LAAM and its metabolites in plasma can be explained on the basis of the strength, nature and magnitude of their binding to plasma proteins.

An unexpected finding in this work has been the weak role played by albumin in the binding of these drugs. Albumin plays the most important role in drug binding by plasma proteins and is usually taken as a model protein for drug studies. It has been previously reported that methadone binds mostly to a globulin fraction (Judis 1976).

Being aliphatic amines, LAAM and its metabolites are protonated at physiological pH. It would be logical to expect the binding of these drugs to the albumin molecule, which contains over 100 carboxyl groups available to form salt like linkages. This is not the case and in turn, the binding occurs to another molecular entity. The suggestion is made that another negatively charged group (possibly a sulfate) may be forming a salt-like linkage with the amine.

The experimental approach used to identify a protein-drug complex is very helpful in cases like this where protein drug complexes are difficult to identify because of the weakness of the association. This approach has been used before to identify plasma

[1] E. Toro-Goyco - unpublished data.

protein calcium complexes in human serum (Toffaletti, Savory, and Gittelman 1977). The results obtained from the Scatchard plot are very significant. It is shown that 1 ml of serum (or plasma) is capable of specifically binding about 3 nmoles of LAAM. If we assume a minimum of one binding site per protein molecule, we conclude that one ml of plasma contains three nmoles of the binding protein. The same volume of plasma contains close to 600 nmoles of albumin, making the binding by albumin a very unlikely possibility. On the other hand, if we suppose the binding globulin to be a very scarce protein in plasma, as suggested by our data, and this protein to be high molecular weight entity of around 400,000 as calculated from SDS gel electrophoresis experiments, we can safely conclude that a protein with a concentration of 1-2 mg/ml plasma could very well be the binding protein. Small changes in the concentration of this binding protein, without a significant change in total plasma proteins could account for marked changes in the LAAM binding capacity of the blood. We have found (work in progress) differences as high as 10-fold in the specific binding affinity for LAAM in the serum of individuals. By the same reasoning these differences could explain the marked differences in dosages required by individuals to react therapeutically.

ACKNOWLEDGEMENTS

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Progress Report From the NIDA Addiction Research Center

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ARC PROGRAM

By September of this year the ARC clinical research program will be relocated into temporary quarters at Baltimore City Hospital (Phase I). The animal and chemical research programs will remain in Lexington for two to three years. In 1981 or 1982, the entire ARC will relocate into refurbished laboratories at Baltimore City Hospitals (Phase II). In the Phase I unit, the ARC will reinstitute clinical abuse potential studies to complement the animal and chemical abuse potential studies. The ARC will maintain its relationship with the CPDD in regard to abuse potential studies. It is doubtful that the ARC will ever be able to clinically assess the number of drugs that it did in the past. For this reason, the ARC will assist the CPDD in developing alternate clinical facilities for these studies.

PCP STUDIES

For approximately the last year and half, the ARC has had an extensive program concerning the problems associated with the abuse of phencyclidine (PCP). As a disease-oriented laboratory, our perspective is to conduct studies to understand the causes, diagnosis, treatment and prevention of PCP abuse.

The research strategy concerning PCP abuse was addressed to the following issues:

1. Reports that indicated PCP showed effects similar to other drugs of abuse including the ability to serve as a reinforcer on self-administration studies.

2. The appearance of PCP precursors as well as PCP homologues and their precursors in street samples.

To date, the ARC scientists have generated an extensive body of data. This progress report will summarize some of these data and some of the conclusions reached by ARC scientists. Because of both space and time limitations, other program activities will not be presented.

Current homologues of phencyclidine consist of substitutes for the phenyl and piperidine rings on the cyclohexane moiety (Table 1). Five homologues of PCP have been identified in illicit samples (TCP, PCM, PCPY, PCE, NPPCA). Three homologues (TCM, PCDEA, NMPCA) were produced as legitimate research drugs. The synthesis of PCP involves the reaction of a carbonitrile precursor with a Grignard reagent such that an incomplete reaction produces a product contaminated by the toxic carbonitrile, PCC (Table 1). PCC, as well as MCC, PYCC, DEACC, was synthesized at the ARC. The two hydroxylated metabolites have also been studied.

Analytic Methods for Identification of PCP Homologues

Thin-layer chromatography (TLC), gas liquid chromatography (GLC) and chemical ionization-mass spectrometry (CI-MS) were investigated as methods for identification of PCP and its homologues, precursors and metabolites. In general, Rf values for these compounds in various TLC systems overlap such that PCP cannot be distinguished from its analogues. GLC was somewhat more specific but no one column or condition tested could resolve the various PCP analogues. On the other hand, with CI-MS all compounds were readily identified.

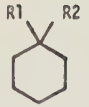
Street Sample Analysis

Small portions of eleven confiscated PCP samples (tablets and powder) were evaluated with GLC and CI-MS. Nine samples contained PCP; the other two contained PCE and TCP. One sample was contaminated by PCC, the toxic precursor.

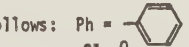
Opiate Receptor Binding (ORB) Studies

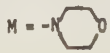
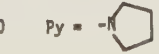
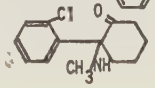
The PCP analogs were studied utilizing standard ORB assays prepared from guinea pig brain. PCP analogs bind sterospecifically but on a much less order than morphine. The potencies of the analogs relative to PCP were similar to those obtained in whole animal assays, suggesting this preparation can be used for studies of structure activity relationships among this class of compounds.

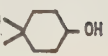
Table 1. Structures of Phencyclidine Homologs and Metabolites



Compound	Name	R1[1]	R2[1]	Precursor
PCP	1-(1-phenylcylohexyl) piperdine	Ph	P1	1-piperidinocyclohexane-carbonitrile (PCC)
TCP	1-[1-(2-thienyl) cyclo-hexyl] piperidine	2-Th	P1	PCC
PCM	1-(1-phenylcyclohexyl) morpholine	Ph	M	1-morpholinocyclohexane-carbonitrile (MCC)
TCM	1-[1-(2-thienyl) cyclohexyl] morpholine	2-Th	M	MCC
PCPY	1-(1-phenylcyclohexyl) pyrrolidine	Ph	Py	1-pyrrolidinocyclohexane-carbonitrile (PYCC)
PCDEA	N,N-diethyl-1-phenyl-cyclohexylamine	Ph	$N(C_2H_5)_2$	1-diethylaminocyclohexane-carbonitrile (DEACC)
NMPCA	N-methyl-1-phenylcyclo-hexylamine	Ph	$NHCH_3$	1-methylaminocyclohexane-carbonitrile
PCE	N-ethyl-1-phenylcyclohexylamine	Ph	NHC_2H_5	-------
NPPCA	N-propyl-1-phenyl-cyclohexylamine	Ph	$NHCH_2CH_2CH_3$	1-propylaminocyclohexane-carbonitrile
KET[1]	2-(O-chloroplenyl)-2-(methylamino)-cyclohexanone			-------
PPC[1]	4-phenyl-4-piperidinocyclohexanol			-------
PCHP	1-(1-phenylcyclohexyl)-4-hydroxypiperidine	Ph	4-HO-P1	-------

[1]Structural abbreviations are as follows: Ph =  P1 = 2-Th =

M =  Py =  KET = 

PPC = 

Chronic Spinal Dog Studies

This preparation allows concurrent analysis of both infra- and supra- spinal drug effects, behavioral effects, and autonomic effects. Data obtained with this preparation include: (1) pharmacologic profiles after acute administration, (2) alteration of drug response by specific antagonists, (3) tolerance and cross-tolerance studies, and (4) dependence and cross-dependence studies. Such data for PCP will allow the determination of similarity of action with other prototypic drugs of abuse. To date, only acute administration studies have been completed.

In doses of 0.125, 0.25, 0.5 and 1.0 mg/kg, PCP was infused over 40 min to five chronic spinal dogs. These doses depressed the flexor reflex, increased heart rate, dilated pupils, retracted the nictitating membrane, increased the latency of the skin twitch and pupillo-constrictor reflexes, and elevated body temperature. The dogs remained quiet but exhibited nystagmus, staring, tracking, and sterotypic head movements. Loss of lateral and medial canthal reflexes and lack of attention to external stimuli indicated anesthesia with the 1.0 and 0.5 mg doses. Opisthotonic posturing and hypersalivation were also produced by these two doses. This single dose pharmacologic profile is distinct from that of LSD, d-amphetamine, delta-9-tetrahydrocannabinol, morphine and pentobarbital although PCP does share some properties in common with each.

The profile does resemble that of SKF-10,047, a prototypic hallucinogenic opioid.

Dog Self-Administration Model

The reinforcing properties of PCP, as well as its analogs and metabolites, are being studied. Intravenous infusions of PCP (3.125, 6.25, 12.5, 25.0 and 50 µg/kg/infusion) were available to the dogs on a FRI schedule during daily 4 hour sessions. Access was given to each unit dose for five daily consecutive sessions with treatments presented in random order.

All five unit doses maintained responding at rates greater than those of saline. The number of infusions decreased as the unit dose increased from 6.25 through 5.00 µg indicating the ability of the dogs to adjust their responses to the magnitude of reinforcement, thereby obtaining approximately the same amount of drug each session. When the unit dose was 3.125 µg/kg/infusion, the dogs failed to respond at a rate to maintain this total drug dose. Preliminary results indicate that dogs respond for ketamine in a similar manner.

Thus, the dog self-administration model appears useful for studying the reinforcing properties of PCP and analogs.

Rotarod Studies

Experiments to determine both the relative potencies and durations of action for phencyclidine-like compounds and their precursors by measuring ataxia were designed to provide information on a nontoxic pharmacological action of these drugs for future comparison to their lethal effects in mice as well as to aid in selecting dose levels for studies in the rat and dog.

Male Swiss Webster mice were tested for their ability to remain on the rod rotating at 5 RPM for a 120 second trial. Following two control trials, each mouse was given an intraperitoneal injection and was tested at 0 minute intervals for 1 hour after injection. Ten mice were used for each dose. Relative potencies were determined from bioassays using peak effect values and with doses expressed as μmole/kg. The following drugs were employed:

(1) (1-phenylcyclohexyl) piperidine HCL (phencyclidine, PCP)
(2) 1-[1-(2-thienyl) cyclohexyl] piperidine HCL (TCP)
(3) 1-piperidinocyclohexanecarbonitrile free base (PCC)
(4) 1-[1-phenylcyclohexyl] pyrrolidine HCL (PCPY)
(5) 1-[1-(2-thienyl) cyclohexyl] pyrrolidine HCL (TCPY)
(6) 1-pyrrolidinocyclohexanecarbonitrile HCL (PYCC)
(7) 1-[1-phenylcyclohexyl] morpholine HCL (PCM)
(8) 1-[1-(2-thienyl) cyclohexyl] morpholine HCL (TCM)
(9) 1-morpholinocyclohexanecarbonitrile HCL (MCC)
(10) N-ethyl-1-phenylcyclohexylamine HCL (PCE)
(11) N,N-diethyl-1-phenylcyclohexylamine (PCDEA)
(12) N-(n-propyl)-1-phenylcyclohexylamine HCL (NPPCA)
(13) 2-(o-chlorophenyl)-2-(methylamine) cyclohexanone (ketamine, KET).

All drugs were dissolved in saline except for PCC which was made up in saline having a pH of 4. The injection volume was 0.01 ml/g of body weight.

The first compounds studied were the cyclohexylpiperidines which included PCP. Setting the potency of PCP equal to 1.00, it was found that its precursor PCC was only .31 times as potent than PCP.

A comparison of the cyclohexylpyrrolidines, again letting the potency of PCP equal to 1.00, showed that PCPY was 1.08 times more potent and TCPY 1.54 times more potent. The precursor for this series PYCC was the least potent having a ratio of 0.22.

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The cyclohexylmorpholine derivatives and precursors were equal to each other in potency although they were only one-fifth as potent as PCP. The actual potencies were: MCC-0.21, PCM-0.18, and TCM-0.17.

The most potent series of compounds investigated was the amine-substituted phenylcyclohexylamines. Compared to PCP, their relative potencies were 2.15 for PCE, 1.52 for PCDEA and 0.82 for NPPCA. A close analogue of the phenylcyclohexylamines is ketamine which is a phenylcyclohexanone. Ketamine was 0.31 times as potent as PCP.

A synopsis of the potencies between these families of PCP analogues showed the phenylcyclohexylamines to be more potent than the equally potent cyclohexylpiperidines and cyclohexylpyrrolidines. Least potent were the cyclohexylmorpholines.

Lethal Dose Studies

Acute lethal dose effects of the carbonitrile precursors and the parent phenylcyclohexyl derivatives of the piperidine, pyrrolidine and morpholine series were determined in order to predict, with respect to the illicit synthesis of these drugs, how contamination with an intermediate precursor might affect the potential toxic effects of the phencyclidine analogue. These studies were conducted in male Swiss Webster mice two weeks after they had been previously used in the rotarod study. Drugs (see Rotarod studies) were administered by i.p. injection and 4 hour LD 50s and potency estimates were determined using the method of Litchfield and Wilcoxon. Ten mice were used for each dose.

Each of the precursors was shown to be more toxic than the parent compound. Using doses expressed as μmole/kg the following potencies relative to the parent derivative were calculated: PCC 1.83 X PCP; PYCC 1.27 X PCPY; and MCC 7.88 X PCM.

Within this group of three precursors, their potencies were almost equivalent: PCC (1.00) - PYCC (.95) $\geq$ MCC (.80).

Among the other derivatives the relationship of their potencies to PCP as determined from the lethal dose studies was as follows: PCPY (1.37) + PCE (1.27) > PCP (1.00) > KET (0.22) > PCM (.19).

Lastly using data from the lethal dose and rotarod studies, the therapeutic index (TI) was calculated for eight compounds using the ratio of the LD50 value to the ED50 value for ataxia in order to provide a measure of their safety. The data broke out into three groups. The precursors possessed the lowest TI's: PCC 3; PYCC 2; and MCC 3. A second group having larger TI's included: PCP 18; PCPY 14; and PCM 18. The highest TI's were those for KET 25.1 and PCE 30.3.

Discriminative Stimulus Properties

The discriminative stimulus properties of phencyclidine were evaluated in rats using a two-choice, discrete trial avoidance task in which rats were injected i.p. with either saline or phencyclidine 1.0 or 3.0 mg/kg 30 minutes prior to the start of the session. Rats were trained until their performance on the appropriate level was 95% correct for 10 consecutive sessions. It was found that rats discriminate PCP from saline in a dose-related manner but the slope in rats trained to the 3.0 mg dose was steeper.

In order to further evaluate the discriminative stimulus properties of PCP, a number of PCP analogs were tested. Studies of PCP and two piperidine analogs, the thienyl derivative (TCP) and the carbonitrile synthetic intermediate (PCC) indicate that TCP produced dose-related PCP-like discriminative stimuli. A dose of 20 mg/kg of TCP was required to produce greater than 90% responding on the PCP-appropriate lever. On the other hand, PCC failed to produce any PCP-appropriate responding even with a dose 3-fold higher than the 3 mg/kg training dose of PCP. Higher doses could not be tested due to toxicity.

In the morpholine chemical family, three similar analogs were tested. Both the phenyl analog (PCM) and the thienyl analog (TCM) produced dose-related PCP-like discriminative stimuli. Doses of 30 mg/kg of PCM and 56 mg/kg of TCM were required to produce greater than 90% responding on the PCP-appropriate lever. Thus, these two compounds were one-tenth to one-twentieth as potent, respectively, as PCP. As in the previous series, the carbonitrile derivative (MCC) failed to produce any PCP-appropriate responding. However, doses as low as 20 mg/kg of MCC produced convulsions.

Within the pyrrolidine chemical family, three similar analogs were tested. The phenyl derivative (PCPY) was approximately equipotent to PCP in producing PCP-like discriminative stimuli. In addition, the thienyl

derivative (PCPY) is equipotent to PCP and PCPY in producing PCP-like discriminative stimuli. As with the two previous carbonitriles, PYCC also failed to produce any PCP-appropriate responding at non-toxic doses.

Several additional PCP derivatives have also been found to produce PCP-like discriminative stimuli. PCE, the N-ethyl analog, is the most potent compound tested to date; a dose of only 1.0 mg/kg of PCE being required to produce at least 90% PCP-appropriate responding. However, the slope of the dose-response curve for PCE appears to be more shallow than that for PCP and this compound is being more extensively tested. The N-propyl analog, which also has appeared on the street, generalizes to PCP and is essentially equipotent to PCP. In addition, ketamine was also found to generalize to PCP and was approximately one-tenth as potent as PCP. Further, the N-diethyl compound has also now been tested and it is approximately equipotent to PCP in producing PCP-like discriminative stimuli.

SKF 10,047 is not a PCP derivative, but is an analog of cyclazocine, a narcotic antagonist with psychotomimetic properties. Interestingly, this compound produced dose-related PCP-like discriminative stimuli and was approximately one-third as potent as PCP. The pharmacologic properties of the discriminative stimulus effects of PCP were further characterized by testing several standard psychoactive drugs from other classes (ketocyclazocine, d-amphetamine, pentobarbital, chlorpromazine, delta-9-THC, morphine, MDA, scopolamine, LSD, physostigmine). None of these drugs produced appreciable levels of responding on the PCP-appropriate choice lever, although each of them produces one or more actions in common with PCP.

Summary and Conclusions of PCP Studies

1. PCP preparations may be contaminated with precursors which are used for synthesis of PCP homologues.

2. Chromatographic methods tested for identification of PCP and homologues showed the following specificity: GC - MS > GLC > TLC

3. Opiate receptor binding (ORB) assay data on PCP homologues correlate well with pharmacologic tests in mouse and rat.

4. Two PCP metabolites are approximately 1/7 as potent and equipotent in the ORB assay.

5. Rotarod studies in the mouse have shown differences in potencies between families of PCP analogues but the magnitude of these differences is not extreme.

6. Acute toxicity studies have demonstrated that the precursors are more toxic than the parent compound.

7. Therapeutic indices indicated that the precursors were less safe than the parent drugs and that PCE was the safest of the analogues tested.

8. Studies in the chronic spinal dog show PCP to be a drug with diverse actions. Within the hallucinogens, PCP most closely resembles a hallucinogenic opioid.

9. PCP can serve as a positive reinforcer in dog self-administration studies, indicating this model may be used to study relative reinforcing properties of PCP homologues.

10. In studies of its discriminative stimulus properties, PCP can produce stimulus control of behavior in the rat.

11. Nine analogues generalized to PCP with clear orders of relative potencies. The precursors did not generalize.

12. Except for the hallucinogenic opioid SKF-10,047, other psychoactive drugs failed to generalize.

13. PCP and analogues are a unique class of drugs.

14. Chronic spinal dog, dog self-administration, and discriminative studies in the rat are useful for:

    (1) Conducting specific studies of the mode of action, the toxicity, and the treatment of PCP abuse, and
    (2) Judging the potential of compounds for PCP-like abuse.

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Drug Dependence Programme of the World Health Organization

Khan, I.

1. It is a pleasure for me to be given the opportunity to inform you of the developments within WHO which I consider will be of interest to this meeting.

Since your last meeting in Baltimore, approximately one year ago, interesting developments have taken place. WHO, having benefitted in the past of the very useful collaboration with the Committee on Problems of Drug Dependence (CPDD), as a body as well as with individual members, has moved a step forward by establishing a more "formal working relationship with the Committee."

2. Drug Evaluation for International Control

It is the United Nations Commission on Narcotic Drugs who has the final authority to decide on recommendations of WHO for scheduling substances under the international drug control treaties. At the 28th Session of the Commission on Narcotic Drugs held in Geneva, 12-23 February 1979, the Commission approved rescheduling the status of methaqualone from Schedule IV to Schedule II of the 1971 Convention. This body also noted with satisfaction the view of WHO that the status of phenobarbital and lefetamine need not be changed.

Nicocodeine (6-nicotinoylcodeine) was approved to be added to the list of drugs in Schedule III of the Single Convention on Narcotic Drugs. This change was requested by the Government of Austria.

Plans for 1979

We have selected for review the following substances for scheduling/rescheduling under the international drug control treaties:

d-Propoxyphene, Tilidine and Sufentanil under the Single Convention on Narcotic Drugs;
Phencyclidine and Mecloqualone under the 1971 Convention on Psychotropic Substances.

3. Some challenges posed to WHO and its Member States by the Convention on Psychotropic Substances, 1971.

(i) Article 2 of the Convention on Psychotropic Substances, 1971, describes briefly the data required for recommending psychotropic substances for international and national control. The 21st Report of the WHO Expert Committee on Drug Dependence[1] gives more details of the methods required to obtain data for this purpose. I wish to refer to certain aspects of those studies where attention is required in a coordinated way by the scientific community, WHO and its Member States. There is a need for coordinated investigations of the major categories of psychotropic substances with respect to:

Self-administration and reinforcement properties, development of CNS tolerance and physical dependence in animals and the development of cross tolerance and cross dependence between new psychotropic substances and substances already controlled.

These studies will provide baseline data against which data obtained with new and similar compounds can be compared. I am aware of the long and valuable role the CPDD has had in screening narcotic substances and antagonists. Would the Committee be willing to undertake a coordinating role in the establishment of agreed procedures for carrying out such tests in psychotropic substances and the allocation of specific testing to the laboratories of individual members? Cooperation with WHO in this venture would be highly appreciated.

(ii) Long-term effects of psychotropic substances on the social and personal functioning, their impact on physical health and the extent to which they positively and/or negatively reinforce other forms of treatment. The 1971 Convention makes it obligatory for WHO, its Member States and the United Nations Commission on Narcotic Drugs, that data on the public health and social problems associated with the use of psychotropic substances be identified, quantified and considered along with data on psychopharmacological tests and the therapeutic usefulness of these substances. Thus, WHO plans to address itself to the assessment of the public health and social problems in an Expert Committee scheduled to meet in September 1980.[2]

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[1] WHO Technical Report Series, No. 618,(1978).

[2] WHO Expert Committee on Drug Dependence, Geneva, 15-20 September 1980.

(iii) As many as half of the patients in general medical practice are prescribed psychotropic drugs in many environments. It is suspected that a significant proportion of these patients are unknowingly dependent on these drugs and it is believed that physicians, including psychiatrists, are often unaware of the "hidden psychotropic drug dependence." The reason is that the symptoms of drug dependence (i.e. anxiety, insomnia, restlessness) are often the target symptoms for which some psychotropic drugs are prescribed. With the increasing use of psychotropic drugs in medical practice there is an urgent need to develop methodological tools to: (a) differentiate drug dependent patients from those who are not, and once these tools are available it will then be possible to (b) assess the true extent of hidden psychotropic drug dependence and to (c) develop collective clinical methods for its management.

4. WHO continues its collaboration with its Member States, especially in developing countries, to develop and strengthen further the programmes on drug dependence. The major activities of these programmes are:

(a) Manpower development and training of personnel.
(b) Strengthening of services and facilities involved in the prevention, treatment and rehabilitation of drug dependent persons.
(c) Development of technology for effective demand reduction of illicit drugs.
(d) Promotion of cooperation between countries in the implementation of drug dependence programmes.

WHO has carried out the above activities in Afghanistan, Burma, Egypt, Iran, Malaysia, Pakistan, Peru, Thailand, and Vietnam.

A study on "drug dependence in socio-cultural context" is also presently being carried out in order to provide guidelines for planning suitable and effective programmes for the treatment and rehabilitation of drug dependent persons.

5. The WHO Research and Reporting Project on the Epidemiology of Drug Dependence is now in its fourth year and is finalizing the methodology development phase. A series of publications are now in preparation which will describe a variety of data collecting methodologies in this field. The methodologies have been tested in a network of collaborating centres, primarily in developing countries and the following reports are expected to be published in 1979 and 1980:

(a) A Methodology for Student Drug Use Surveys
(b) Core Data Items in Epidemiological Studies of Drug Dependence.
(c) The Use of Reporting Systems on Drug Abuse.

(d) General Population Surveys on Drug Abuse
(e) Intensive Case Finding and Monitoring of Drug
(f) Drug Use Surveys of Special Populations at Risk, including Unemployed and Working Youth.
(g) Evaluation of Drug Dependence Treatment Methods
(h) WHO Guidelines for Collecting Existing Information on Dependence Producing Substances.

At the meeting of collaborating investigators in April of this Year in Malaysia, the project was evaluated and the future directions proposed, including the application of these methodologies on the country level.

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Fifty Years of International Control of Dependence-Producing Drugs

Kaymakcalan, S.

It is my pleasure and honour to greet you as the representative of the International Narcotics Control Board (INCB) of the United Nations.

Your Committee was born 50 years ago as an advisory Committee on drug addiction of the National Academy of Sciences-National Reseach Council. It is a happy coincidence that international control of narcotic drugs was also established exactly 50 years ago.

The first international organ concerning the control of legitimate use of narcotics which was the Permanent Control Board, was created by the Geneva Opium Convention of 1925 and started to work in 1929. It was primarily concerned with monitoring manufacture of, and trade in, narcotic drugs through the establishment of a statistical reporting system.

Over the years it became necessary to enlarge the scope of the 1925 Convention to place under control some new substances and also to combat illicit use and traffic of psychoactive substances. Seven additional treaties were signed in the years of 1931, 1936, 1948, 1953, 1961, 1971, and 1972. The last three are the most important and are known as the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1972 Protocol Amending the Single Convention.

At present the number of States which are parties are 110 for the Single Convention, 57 for the Convention on Psychotropic Substances, and 66 for the 1972 Protocol. The INCB, which was created by the Single Convention, is the successor to the Permanent Control Board and the Drug Supervisory Body. The latter had been established by the 1931 Convention to ensure control over future legal national requirements of narcotic drugs. This became the "estimates" system.

As it is presently composed, the INCB has thirteen members who are elected by the United Nations Econonomic and Social Council and who act in their personal capacity. Within the legal framework of the

treaties, the Board's main duties are:

1) to monitor the international trade in both narcotic and psychotropic substances through the administration of the estimates (applicable to narcotic drugs only) and the statistical systems with a view to preventing any country from becoming a center of illicit traffic;

2) to endeavour, on the other hand, to ensure that there is a balance between the licit supply of, and demand for, narcotic drugs;

3) to recommend, in the event of important breaches of the relevant treaties, an embargo on the import of drugs, export of drugs, or both, from or to the country or territory concerned; I am glad to say that this has never been fully invoked because all countries are normally ready to cooperate.

4) to recommed assistance to countries which need it to help them comply with their international treaty obligations.

5) to address itself to public opinion world-wide through the publication of its annual report.

The INCB works in close cooperation with the Commission on Narcotic Drugs, the Division of Narcotic Drugs of the U.N., the United Nations Fund for Drug Abuse Control and the WHO.

In spite of these combined efforts it is a fact that there is a growing problem of abuse of dependence-producing substances in many parts of the world. However, it should not be forgotten that if international treaties and endeavours did not exist, the world's situation would be much worse.

A few examples may clarify this situation. Between 1925 and 1929 evidence documented by the Secretariat of the League of Nations showed that at least 100 tons of morphine-type dependence producing drugs passed into the illicit traffic by diversions from duly authorised licit manufacture. The total world legitimate needs were then approximately 39 tons of morphine equivalent per year. The huge amounts of narcotics had been obtained by illicit traffickers from authorized manufacturers. During 1927 and the first three months of 1928 a single factory in Europe had exported 860 kg. of morphine, 2.711 kg. of heroin and 40 kg. of cocaine to a single country for illicit purposes.

Since international treaties became progressively operative there have been no,or negligible, leakages of narcotics from licit sources to the illicit traffic.
During the last decade we have seen an almost similar situation with amphetamines. Although many industrialized countries are still not parties to the 1971 Convention, there have been considerable reductions in the manufacture of amphetamines in many countries

following the terms of this Convention.

Before closing my remarks I may say that in the struggle against the abuse of dependence-producing substances we are not pessimistic. At least one may think that international efforts have had some positive effects in reducing the supply of these drugs. However, as regard the etiology, treatment and rehabilitation of drug dependence there are still many things to be learned. Therefore the scientific contributions of your Committee are very important to the international community, and I am sure that your achievements will help to reduce the suffering of mankind.

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A New Synthetic Codeine Substitute: (-)-3-Phenoxy-N-Methylmorphinan

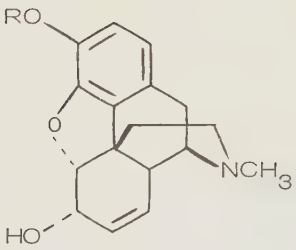
Mohacsi, E.; Leimgruber, W.; Baruth, H.

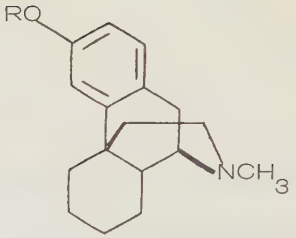
INTRODUCTION

In recent years, there has been a growing concern in the United States that a serious shortage of analgesics prepared from opium may develop in the event of a major national emergency[1]. Consequently, there has been considerable interest to provide alternate sources for these drugs or to complement and possibly replace them with synthetic substitutes. In connection with this latter approach directed at the search for a synthetic codeine substitute with reduced addiction liability, we undertook a number of years ago the synthesis of 3-O-t-butylmorphine (3) and (-)-3-t-butoxy-N-methylmorphinan (6)[2]. Our rationale for preparing this novel codeine and levomethorphan analog was based on the expectation that a tertiary butyl group on phenolic oxygen would prevent their in vivo metabolic conversion to morphine (1) and levorphanol (4), respectively, thus eliminating the pharmacological effects of these metabolites.

Pharmacological evaluation revealed that 3-O-t-butylmorphine (3) is active in the writhing but not in the tail-flick test, whereas (-)-3-t-butoxy-N-methylmorphinan (6) shows activity in both tests. The virtual lack of analgesic activity in the case of the codeine analog 3 has been explained in terms of its blocked metabolic pathway to morphine[3]. However, any interpretation must take into account the subsequent finding[4] that both analogs, despite the presence of a bulky tertiary butyl group, show similar binding to the opiate receptor when compared to codeine (2) and levomethorphan (5), respectively.

Since the potentially interesting levomethorphan analog 6 was





1 R = -H
2 R = $-CH_3$
3 R = $-C(CH_3)_3$

4 R = -H
5 R = $-CH_3$
6 R = $-C(CH_3)_3$
7 R = $-C_6H_5$

unsuitable for development in view of its instability in acids, we shifted our synthetic efforts towards the preparation of aryl ethers of levorphanol (4) such as (-)-3-phenoxy-N-methylmorphinan (7) which had not been previously reported. We hoped to find within this class of compounds a codeine-like analgesic with reduced addiction liability because the presence of a lipophilic phenyl group was expected to facilitate transport to narcotic receptor sites while preventing metabolic conversion to levorphanol. An additional attractive feature of these aryl ethers was their anticipated chemical stability under conditions which cause degradation of codeine to morphine, thus providing a safeguard against abuse.

METHODS

CHEMISTRY

Ullmann reaction[5] of levorphanol with bromobenzene in pyridine in the presence of potassium carbonate and copper gave (-)-3-phenoxy-N-methylmorphinan (7). The substituted O-aryl-N-methylmorphinans 8-19 were prepared by this method from 4 and the appropriate aryl halides[6].

When 7 was treated with O-dealkylating agents commonly employed in the morphine and morphinan series, such as pyridine hydrochloride[7] at 220° for 25 minutes, 48% hydrobromic acid in refluxing acetic acid[8] for 6 hours, or boron tribromide in chloroform[9] at room temperature, only starting material was isolated. Attempted ether cleavage with sodium in liquid ammonia[10] also resulted in the recovery of the starting

material 7 in high yield.

PHARMACOLOGY

Analgesic measures

Phenylquinone-writhing test. The writhing test described by Siegmund et al.[11] as modified by Hendershot and Forsaith[12] was used to test the compounds for analgesic activity in mice. The ED_{50} and their 95% confidence limits were determined by the method of Litchfield and Wilcoxon[13]. The test results are shown in Tables 1 and 2.

Tail-flick method. The antinociceptive potency of the compounds was assessed using the tail-flick method of D'Amour and Smith[14] as described by Dewey and Harris[15] in mice and rats. The ED_{50} and 95% Fiellers' limits were computed by the Berkson Minimum Logic Chi-Square method[16]. The test results are presented in Tables 1 and 2.

Binding assays. Interaction of the compounds with the opiate receptor in whole rat brain homogenates was measured by assaying the displacement of [^{3}H] naltrexone from specifically bound sites as described before[17].

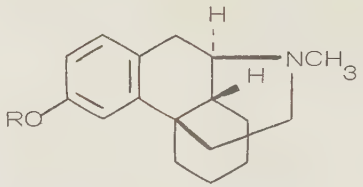
The concentration of the test compound necessary to displace one-half of the stereospecific [^{3}H] naltrexone binding (IC_{50})[4] is shown in Table 2.

RESULTS AND DISCUSSION

Tables 1 and 2 summarize the results obtained in various test procedures[11-17] with the new aryl ethers (compounds 7-19). Activities of these compounds were compared with those of morphine (1), codeine (2), levorphanol (4), and levomethorphan (5). As Table 1 indicates, (-)-3-phenoxy-N-methylmorphinan (7) has about twice the analgesic potency of codeine in mice. When the phenoxy group in 7 was replaced by a pyridyloxy group (compound 8), a moderate increase in analgesic activity was observed. Except for a p-hydroxy group (compound 12), substituents on the phenyl ring did not significantly alter analgesic potency.

As shown in Table 2, compound 7 interacts with the opiate receptor with an affinity comparable to codeine and levomethorphan[4,17]. The analgesic potency of 7 is about twice that of codeine when administered subcutaneously in both the phenylquinone writhing[11,12] and tail-flick assays[14,15] in mice, but 7 is about 10 times more potent than codeine in the writhing and

Table 1. Analgesic Activities of O-Arylmorphinans



Comp	R	Analgesic act.[a], ED_{50}, mg/kg Writhing	Tail-flick
7[b]	C_6H_5-	1.25 (0.78-2.00)[g]	19.71 (17.28-22.16)
8[b]	2-pyridyl-	1.1 (0.61-1.98)	10.08 (8.95-11.35)
9[c]	4-$CH_3OC_6H_4$-	2.1 (1.08-4.10)	24.98 (21.99-28.96)
10[d]	3-$CH_3OC_6H_4$-	2.5 (1.43-4.38)	39.74 (33.21-51.54)
11[d]	2-$CH_3OC_6H_4$-	0.49 (0.26-0.93)	24.40 (21.27-30.17)
12[c]	4-HOC_6H_4-	1.3 (0.65-2.60)	6.69 (4.88-8.17)
13[b]	3-HOC_6H_4-	9.0 (4.50-18.00)	80.14 (56.17-159.14)
14[b]	2-HOC_6H_4-	1.8 (0.90-3.60)	11.44 (10.95-12.06)
15[c]	4-$CH_3C_6H_4$-	23.0 (13.94-37.95)	----
16[c]	2-$O_2NC_6H_4$-	2.8 (1.65-4.48)	----
17[c]	4-FC_6H_4-	1.0 (0.38-2.65)	37.26 (33.15-42.76)
18[b]	3-FC_6H_4-	1.85 (1.00-3.00)	71.00 (58.36-92.13)
19[d]	2-FC_6H_4-	3.0 (1.36-6.60)	23.31 (20.49-26.98)
1[e]	Morphine	0.46 (0.26-0.83)	4.06 (3.78-4.41)
2[f]	Codeine	2.3 (1.21-3.91)	38.97 (35.31-42.79)

a) Tested sc in mice. b) Tartrate. c) Hydrochloride. d) Oxalate. e) Sulfate. f) Phosphate g) Numbers in parenthesis are the 95% confidence limits.

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Table 2. Analgesic Activities and Opiate Receptor Affinities

Compound	Route	Analgesic act.[a], ED_{50}, mg/kg		Binding affinities[g,h] [^{3}H] Naltrexone (10^{-9}) $IC_{50} \times 10^6$ (tris buffer)
		Writhing	Tail-flick	
Morphine[b]	sc	0.46 (0.26-0.83)[f]	4.06 (3.78-4.41)	0.027
	po	2.5 (1.40-4.45)	31.20 (26.30-35.73)	
Codeine[c]	sc	2.3 (1.21-3.91)	38.97 (35.31-42.79)	10.0
	po	24.0 (13.71-42.00)	119.03 (105.16-132.21)	
Levorphanol[d]	sc	0.11 (0.06-0.22)	1.21 (1.13-1.31)	0.004
	po	1.4 (0.70-2.80)	8.50 (7.22-10.25)	
Levomethorphan[e]	sc	0.64 (0.34-1.22)	6.78 (6.23-7.42)	2.0
	po	1.5 (1.32-1.71)	5.27 (4.49-6.17)	
7[d]	sc	1.25 (0.78-2.00)	19.71 (17.28-22.16)	5.0
	po	2.3 (1.22-4.32)	51.68 (43.72-62.41)	

a) Tested sc and po in mice. b) Sulfate. c) Phosphate. d) Tartrate. e) Hydrobromide f) Numbers in parenthesis are 95% confidence limits. g) Binding was performed using rat brain homogenate. h) Expressed as the concentration of compound required to inhibit stereospecific [^{3}H] naltrexone binding by 50%.

approximately twice as active in the tail-flick assay when administered orally. In the rat tail-flick test[14,15] it is equal to codeine (ED_{50} 12.2 mg/kg, vs. 12.3 mg/kg) by the subcutaneous route, whereas it is approximately five times more potent than codeine upon oral administration (ED_{50} 25.68 mg/kg and 126.03 mg/kg respectively). As expected, the analgesic action of 7 in the rat tail-flick test (25 mg/kg sc) is inhibited by pretreatment with naloxone (2 mg/kg sc). The duration of analgesic activity observed for 7 was at least twice that of codeine when administered at equiactive doses in both the mouse and rat tail-flick assays. An additional important feature of 7 is the finding of Dewey et al.[18] that it has considerably less physical dependence liability than codeine. This is evidenced by substitution experiments in rats in which codeine, but not 7, substituted for morphine in morphine-dependent rats, while 7 substituted only partially for codeine in codeine-dependent rats. These studies also showed that 7 is devoid of primary physical dependence in rats in contrast to codeine and morphine[18]. Finally, preliminary metabolic studies of 7 in rats identify compound 12 as the major metabolite while levorphanol and 3-phenoxynormorphinan were detected as the minor metabolites[19].

In conclusion, (-)-3-phenoxy-N-methylmorphinan (7) is an orally effective analgesic comparable to codeine except for its decreased physical dependence liability and its longer duration of action. Although this compound is a levorphanol ether it cannot be converted by conventional reactions to levorphanol, thus providing a safeguard against abuse. Furthermore, since it is prepared by total synthesis, adequate supplies can be assured at reasonable cost. Preclinical studies of this potential codeine substitute are under way in preparation for clinical trials in man.

Acknowledgment. We are indebted to Dr. E.J. Simon, Department of Medicine, New York University Medical Center, New York 10016, for the binding affinity data. We are also grateful to Mr. T. Hayes, Mrs. D. Kelly, Mr. R. Marino and Mrs. J. Ploski for their technical assistance and to Dr. J. Sepinwall for providing analgesic data. Finally, the authors wish to thank Mr. L. Berger for his stimulating suggestions and valuable discussions.

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Stereospecific and Potent Analgetic Activity for Nantradol—A Structurally Novel, Cannabinoid-Related Analgetic

Milne, G. M.; Koe, B. K.; Johnson, M. R.

SUMMARY

Nantradol is a structurally novel, cannabinoid-related analgetic with two to seven times greater potency than morphine across a battery of analgetic tests. Despite this morphine-like analgetic profile, nantradol is devoid of interactions at the opiate receptor. Nantradol has a total of five asymmetric centers and has heretofore been studied as a 50:50 mixture of two diastereomers, both of which possess the *trans* 6a, 10a stereochemistry and have β-oriented substituents at positions 6 and 9. Evidence is provided that, in common with the opiates, the analgetic actions of nantradol are stereospecific, the majority of the activity residing in a single levorotatory isomer. The stereospecificity and potency of the analgetic effects of the nantradol series suggests a highly specific interaction at an as yet unidentified receptor.

INTRODUCTION

Despite long-standing anecdotal evidence suggestive that marijuana preparations have analgetic properties in man (Li 1974; Rossi 1970), reports of the analgetic activity of the natural cannabinoids can best be described as equivocal (Mechoulam 1973; Hill et al. 1974; Milstein et al. 1975). However, recently it has been reported that oral Δ^9-tetrahydrocannabinol (Δ^9-THC, Figure 1), the proposed active constituent of *Cannabis satavia*, at 10 and 20 mg provides pain reduction equivalent to codeine (60 and 120 mg) with marked sedation being a primary side effect at the higher doses of Δ^9-THC (Brunk et al. 1975; Noyes et al. 1975; Noyes et al. 1976). Certainly in laboratory animals, a number of investigators have reported that Δ^8- and Δ^9-THC exhibit analgetic properties, in some cases comparable to morphine (Sofia et al. 1973; Buxbaum 1972; Chesher et al. 1973; Kaymakcalan, Turker, and Turker 1974). However, Dewey et al. (1972) could not show a significant antinociceptive effect for Δ^9-THC in the mouse tail flick test.

It is perhaps fitting that one of the most revealing probes into the analgetic activity of cannabinoid molecules was carried out in the

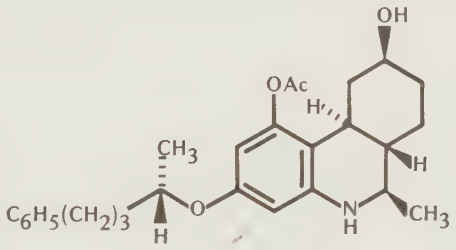
laboratories of Everette May, an acknowledged leader in the field of opiate analgesics. In 1974, May and Wilson (1974) postulated that the analgetic activity of Δ^8- and Δ^9-THC was due to their 11-hydroxy metabolites. They supported this conclusion by the observation that the 9-nor derivatives, which cannot be transformed into the 11-hydroxy metabolites, lack significant analgetic activity but exhibit dog ataxia and cardiovascular profiles nearly identical to Δ^8- and Δ^9-THC (Wilson and May 1974; 1975). During these studies (-)-9-nor-9β-hydroxyhexahydrocannabinol (HHC) was prepared and found to be analgetic with activity in the mouse hot plate test nearly equal to that of morphine (Wilson et al. 1976). Their finding that analgetic activity was a discrete, dissociable feature of the cannabinoid molecule considerably buttressed the historical case for cannabinoid analgesia.

Recently, we have reported (Milne et al. 1978) on the analgetic activity of an even more potent and structurally distinct cannabinoid related analgetic, nantradol, with activity two to seven-fold greater than morphine across a variety of animal tests. Despite an opioid-like spectrum of analgetic activity, nantradol does not bind to the opiate receptor *in vitro*. In distinction to Δ^9-THC, nantradol exhibits reduced analgetic tolerance development and an improved ratio of analgetic to cannabinoid-like behavioral activity.

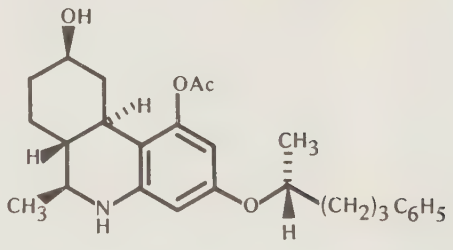
Nantradol has a total of five asymmetric centers; however, owing to its defined stereochemistry at positions 6, 6a, 9 and 10a, it is an approximately equal mixture of only four of the possible 32

Figure 1. Stereoisomers comprising nantradol

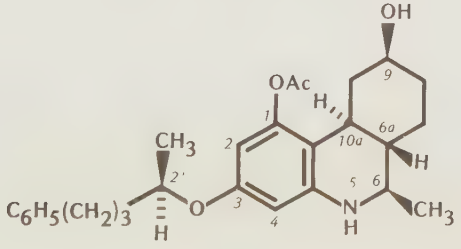
Diastereoisomer A



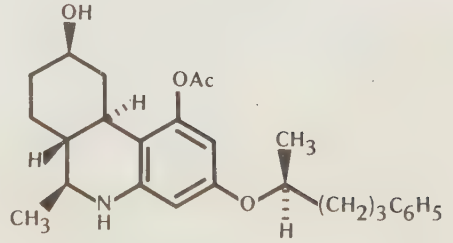
(+)-2'(S),6(R),6a(S),9(S)10a(S)
(CP-53,870-1)



(-)-2'(R),6(S),6a(R),9(R)10a(R)
(CP-50,556-1)



(+)-2'(R),6(R),6a(S),9(S),10a(S)



(-)-2'(S),6(S),6a(R),9(R)10a(R)

Diastereoisomer B

isomers. Nantradol has heretofore been studied only as a 50:50 mixture of the two racemic diastereoisomers indicated in Figure 1, both of which possess the *trans* 6a, 10a stereochemistry and have β-oriented substituents at positions 6 and 9. In the present paper, we will provide evidence that the analgetic actions of nantradol are stereospecific, both with respect to the nucleus and the C-3 side chain.

METHODS

Subjects: Mice used in most of the studies were Charles River males, Swiss CD strain (17-21 g). Mice in the 2-phenyl-4-benzoquinone abdominal stretching experiment were Carworth males, albino CF-1 strain, weighing 11-15 g. Rats were Charles River males, Sprague-Dawley CD strain weighing 180-200 g unless otherwise noted.

Materials: Δ^9-Tetrahydrocannabinoid (Δ^9-THC) was supplied courtesy of Ms. Jacqueline R. Porter of NIDA. Nantradol [(+)-1-acetoxy-5,6,6aβ,7,8,9,10,10aα-octahydro-9β-hydroxy-6-β-methyl-3-(5'-phenyl-2'-pentyloxy)-phenanthridine hydrochloride)] and its stereoisomers (Figure 1) are a product of Pfizer Central Research. Pentazocine was graciously donated by Winthrop Laboratories.

Except where otherwise noted, nantradol, Δ^9-THC and comparative standards were dissolved and administered to rodents in a vehicle consisting of 5 percent ethanol, 5 percent Emulphor-620 and 90 percent saline. This vehicle alone served as the control treatment. Doses of salts were calculated from weights of the salt and not of the base. Solution concentrations were varied to allow a constant injection volume of 10 ml/kg of mouse and 5 ml/kg of rat.

Statistics: In several analgesic and other studies, data were first calculated as the "% maximal possible effect," or % MPE. For most studies, this datum was calculated as follows:

$$\% \text{ MPE} = \frac{\text{mean test value - mean control value}}{\text{maximum possible value - mean control value}} \times 100$$

For the PBQ study, it was calculated as follows:

$$\% \text{ MPE} = \frac{\text{mean control stretches - mean test structures}}{\text{mean control stretches}} \times 100$$

In either case, % MPE may be interpreted as the mean degree of analgesic or other effect on a given test. As it approaches 100 percent, it indicates that the drug produced the maximum effect possible; as it approaches 0 percent, it indicates that the drug produced no effect. In many studies, mean % MPE data were subjected to a linear least squares regression analysis, from which an "MPE_{50}" was determined. MPE_{50} may be interpreted as the best estimate of the dose of a substance at which 50 percent of the maximum possible effect could be observed on a given test.

Tests of analgesia. Blockade of abdominal stretching after phenylbenzoquinone (PBQ test): Pairs of Carworth CF-1 mice were injected

with 2 mg/kg of PBQ i.p. and placed in a lucite box maintained at 40°C by a thermostatically controlled water bath. Drug pretreatment times were 1 hr unless otherwise specified. Starting 5 min later the animals were observed for 5 min and the number of abdominal stretching responses per animal was recorded. A stretch was considered to represent an intermittent contraction of the abdomen, hind limb extension, pelvic rotation or opisthotonos. The degree of analgesic protection was calculated on the basis of the suppression of writhing relative to control animals run on the same day (% MPE), as described above.

Mouse tail-flick test: Tail-flick testing in mice was modified after the D'Amour and Smith (1941) procedure.

Haffner tail-pinch test: A modification of the procedure of Haffner (1929) was used to ascertain drug effects on the aggressive attacking responses elicited by a pressure stimulus pinching the tail.

Flinch-jump test: A modification of the flinch-jump procedure (Evans 1961; Tenen 1968) was used for determining pain thresholds following drug administration.

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Table 1. Comparative Doses Producing 50 Percent of the Maximum Possible Analgetic Effect

Compound	MPE_{50} (mg/kg sc) at Time of Estimated Peak Activity (95% Confidence Limits			
	PBQ Writhing[b]	Tail Flick[b]	Rat Tail Pinch[c]	Flinch Jump[c]
Morphine[a]	0.9 (0.4-1.3)	2.9 (1.4-7.0)	4.3 (3.5-5.8)	10.3 (6.6-13.8)
Δ^9-THC	9.1 (5.4-12.3)	55 (32.4-218.2)	~133	83 (47.8-122)
CP-44,001-1	0.4 (.33-.56)	0.7 (.47-1.1)	1.0 (.57-1.6)	1.4 (.89-3.1)
Diastereoisomer A	0.2 (.11-.34)	0.2 (.17-.31)	0.7 (.53-.91)	.30 (.22-.38)
Diastereoisomer B	1.7 (.79-4.5)	2.4 (1.7-4.2)	14.2 (8.3/46.8)	2.4 (1.5-5.1)
CP-50,556-1	0.1 (.05-0.1)	0.2 (0.1-0.4)	0.3 (0.07-.34)	0.3 (0.2-0.5)
CP-53,870-1	6.5 (6.4-6.6)	>10	>10	NA
Pentazocine[a]	7.4 (1.3-13)	>56	>56	>56
Aspirin (po)	123 (106-132)	>100	>100	>100

[a]All test results at 0.5 hr post dose
[b]Values at 1 hr post dose
[c]Values at 2 hr post dose

RESULTS

Analgetic effects in rodents. Nantradol exerted analgetic effects against each of the nociceptive challenges exemplified in Table 1. The pattern of antinociceptive activity seen for nantradol was similar to that found for morphine but quite distinct from that of the antiinflammatory and narcotic antagonist standards. Nantradol was from 20 to 100 times more potent than Δ^9-THC, the higher ratios reflecting superior activity in the more stringent tests for analgesia.

Comparison of the two diastereomeric components of nantradol (isomers A and B) indicated that most, but not all, of its analgetic activity resides in the A diastereomer. The levorotatory isomer of diastereoisomer A (CP-50,556) was likewise shown to account for the preponderance of both isomer A and nantradol analgetic activity.

DISCUSSION

Nantradol has a number of structural and pharmacological features which distinguish it from both the opiates and cannabinoids. The most notable structural differences are the absence of a pyran oxygen, the presence of a weakly basic nitrogen and the introduction of an oxygen-containing C-3 side chain. Nantradol is considerably more potent (20 to 100-fold) than Δ^9-THC as an analgetic, and as previously reported, nantradol also has substantially reduced tolerogenic activity relative to Δ^9-THC (Milne et al. 1978).

The substantial potency exhibited by these compounds suggests that they are acting rather specifically to produce their analgetic effects, and in fact, Wilson and May (1976) had previously found that the activity of HHC is stereospecific. However, the C-3 side chain of HHC contains no asymmetric centers. In the case of nantradol, we have introduced an asymmetric center in the C-3 side chain. The results reported herein demonstrate that stereospecificity of action also extends to this region of the molecule.

Since as tested nantradol is a mixture of four isomers - a pair of racemic diastereomers present in essentially equal amounts, the first step toward identifying the major active isomer was the separation of nantradol into its component diastereomers - herein designated diastereoisomers A and B. Diastereomer A is at least 10-fold more potent than its C-3 side chain counterpart diastereomer B in analgetic tests. These results clearly suggest that isomer A contains the enantiomer responsible for the majority of nantradol's analgetic activity. Separation of isomer A into its two optically active components demonstrates that the levorotatory isomer, CP-50,556-1, possesses the largest portion of the analgetic activity of nantradol, being four- and two-fold more potent than nantradol and diastereoisomer A, respectively.

The demonstration that CP-50,556-1 produces opiate-like analgesia stereospecifically without binding to the opiate receptor suggests that these new derivatives act stereospecifically at a novel, as yet unidentified, site of action.

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8β-Alkyl-N-Cycloalkyl-Dihydro-Codeinones and -Morphinones as Analgesic Narcotic Antagonists

Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Schut, R. N.

The finding of potent analgesic activity in a series of tertiary alcohols derived from Diels-Alder adducts of thebaine prompted the proposal of a lipophilic site on the opiate receptor (Lewis, Bentley, and Cowan 1971). This new lipophilic site was in addition to the previously proposed anionic site, the cavity for C-15 and C-16 and a flat surface for the aromatic A ring. This lipophilic site was proposed to extend from the vicinity of C-7 and C-8 in the C ring of the morphine nucleus. This site must be of great importance in the binding of 6,14-*endo*-ethenotetrahydrooripavines to the opiate receptor as demonstrated by the high analgesic potency of this series and the affinity with which these compounds bind to isolated receptors. We wished to utilize this site in the design of novel, potent analgesic narcotic antagonists.

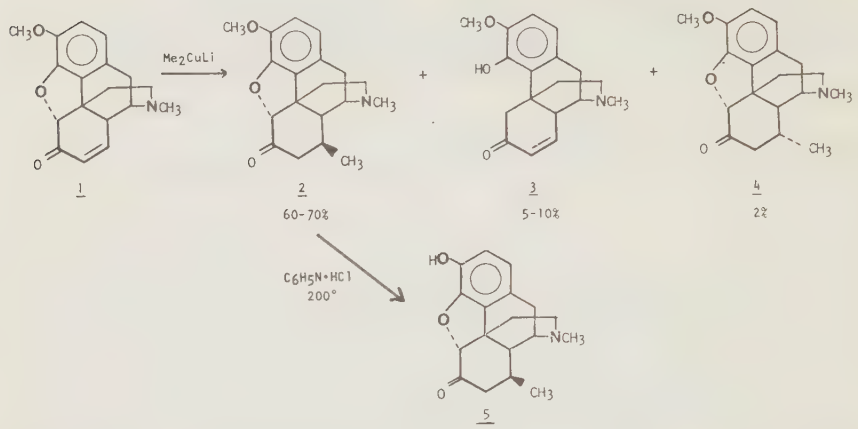
In order to utilize this site on the opiate receptor, we initiated a study to determine the effect of lipophilic alkyl substitution in this region of the morphine nucleus. At the onset of our work, it appeared that carbon-carbon bond formation in the C ring could be most easily accomplished at carbon 8 using a 1,4- conjugate addition reaction. In particular, the use of lithium organo copper reagents (Posner 1972) attracted our attention as an efficient method for introducing various alkyl groups at this position of opiate derived α,β-unsaturated ketones.

We also knew that a narcotic antagonist component of action could be incorporated into the newly synthesized molecules by replacement of the N-methyl group with moieties such as cyclopropylmethyl, cyclobutylmethyl or allyl (Eddy and May 1973). This paper describes our work on the conjugate addition of alkyl groups to codeinone.

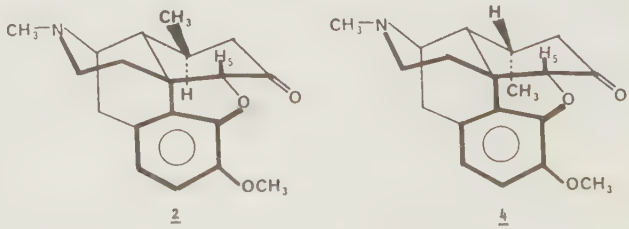
Codeinone (1) was easily prepared from thebaine by modification of a reported method (Gavard et al. 1965). Addition of a benzene solution of codeinone (1) to 1.25 equivalents of lithium dimethyl cuprate in ether gave a mixture of products. The major product, identified as 8β-methyl-7,8-dihydrocodeinone (2) was obtained in crystalline form from the reaction mixture in ~ 50 percent yield. Additional 2 was obtained as the fastest migrating component on

chromatography of the mother liquors. The next product eluted was thebainone-A (3), a 4,5-epoxy cleaved product, identified by comparison with an authentic sample (Sawa, Horiuchi, and Tanaka 1965). The most polar product, obtained only in small amounts, was identified as the 8α-methyl isomer 4.

Scheme 1



The structures of the alkylated products 2 and 4 were proven by mass spectrometry and nmr studies. The mass spectral fragmentation of both isomers showed a parent ion peak followed by loss of a methyl radical. The remainder of the mass spectra were similar to those reported for codeinone. The configuration of the methyl group in isomers 2 and 4 were definitively proven by nmr spectroscopy. The methyl group of 4 was observed at δ 0.40 in $CDCl_3$ solution. This position is upfield by about 0.6 δ from the methyl group signal of



	2	4
δCH3	1.02 (unsymm d) J = 6 Hz	0.40 (d) J = 7 Hz
δH5	4.65 (s)	4.73 (s)
δaromatic	6.68 (s)	6.68 (d) J ~ 1 Hz

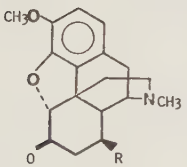
the major product 2. The upfield shift in 4 may be attributed to the anisotropic effect of the aromatic A ring which can occur only if the methyl group occupies the axial or α orientation. Having established the configuration of the methyl group in the minor product as α, and hence, in the major product as β, we observed

several other differences in these spectra. The singlet for the H5 proton of the minor α product was observed at a position slightly downfield from that of the major product. Secondly, the aromatic region of 2 was observed as a singlet whereas the aromatic region of 4 was a sharp narrow doublet with a coupling of ∿ 1 Hz. This difference in the aromatic region was also observed in other α-β pairs which we have isolated. In cases where we isolated only one isomer, the shape of the aromatic region was used to confirm the stereochemistry at C-8.

The series of 8-alkyl-7,8-dihydrocodeinones we have prepared are listed in Table 1. We obtained in pure form both the α and β isomers of 8-methyl, 8-ethyl- and 8-propyl-dihydrocodeinone, the β isomers in each case being the predominant product. For the remaining compounds listed in Table 1, we isolated only the β product. Yields for this isomer ranged from a low of 50 percent to a high of ∿ 90 percent. The yields in the conjugate addition reaction appear to be highly dependent on the purity of the alkyl lithium compound used to prepare the organo copper complex and in the formation and thermal stability of the lithium diorganocuprate.

Table 1

ED_{50} (mg/kg)



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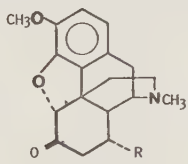

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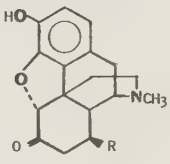


5

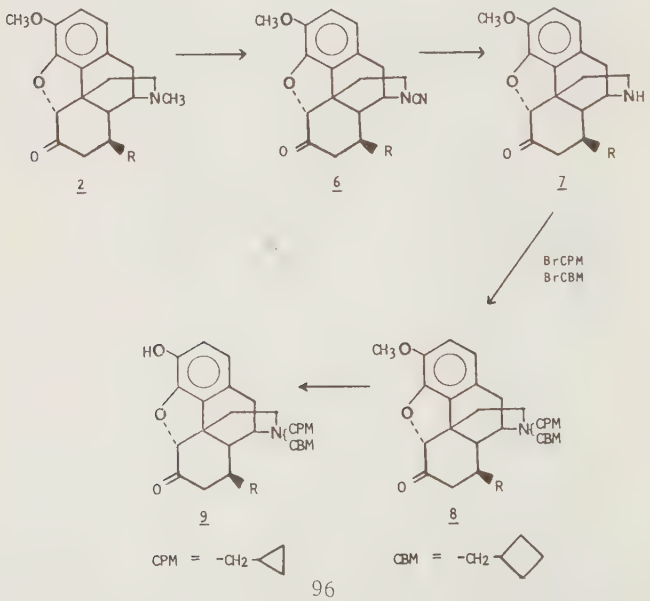
CMPD	R	MOUSE WRITHING	RAT TAIL FLICK
2a	Methyl	1.7	3.6
2b	Ethyl	0.64	7.4
2c	Vinyl	5.0	47.0
2d	Cyclopropyl	15.8	> 10
2e	*n*-Propyl	6.6	-
2f	*i*-Propyl	8.2	> 20
2g	*i*-Propenyl	> 20	-
2h	*n*-Butyl	10.6	> 20
2i	*t*-Butyl	6.9	> 10
2j	δ-Butyl A	5.0	-
2k	δ-Butyl B	> 10	-
2l	*n*-Octyl	11.6	> 10
2m	Phenyl	> 20	-
Dihydrocodeinone (R=H)		1.06	2.35
4a	Methyl	0.71	1.32
4b	Ethyl	0.98	> 10
4e	*n*-Propyl	> 10	> 10
5a	Methyl	0.08	0.53
5b	Ethyl	0.13	0.35
Dihydromorphinone (R=H)		0.08	0.43

Several of these 8β alkyl-dihydrocodeinones were O-demethylated to the corresponding morphinones. The transformation of 2 to 5 was accomplished by heating 2 with pyridine hydrochloride at 200° for 1 to 2 hours.

The compounds prepared were tested in both the acetic acid mouse writhing (Whittle 1964) and heat-induced rat tail flick (Harris and Pierson 1964) assays for analgesic activity. The results of these assays are indicated in Table 1. The 8-alkyldihydrocodeinones (2a-b and 4a-b) and the 8β-alkyldihydromorphinones (5a-b), where the 8 alkyl group is methyl or ethyl, have about the same potencies as dihydrocodeinone (2, R = H) or dihydromorphinone (5, R = H). Unexpectedly, introduction of a side chain larger than ethyl, for example n-propyl (2e), or the introduction of unsaturation (2c) or an aromatic group (2m) at the 8 position cause a drop in potency. One of the stereoisomers of the secondary butyl compounds (2j) was active, whereas the other was inactive. The 8α-dihydrocodeinones (4a-b) were also as active as the reference dihydro compounds, but the activity again rapidly falls off when the 8α group is larger than ethyl. These data indicate that incorporation of a small alkyl group at the C-8 position of morphine does not substantially alter the analgesic effect of the N-methyl compounds.

We next determined the effect of short 8β-alkyl-substituents in N-substituted dihydro-codeinones and -morphinones. The agonists 2 were converted to N-cycloalkylmethyl compounds as outlined in Scheme 2. Treatment of 2 with cyanogen bromide gave the N-cyano compounds 6 which were hydrolyzed to the nor-compounds 7 by refluxing in 2 N HCl. Alkylation with the appropriate bromide gave 3-methoxy-N-antagonists 8. These substituted codeinones were converted to morphinones 9 by pyridine hydrochloride treatment. The corresponding 8-hydrogen antagonists (R = H) were prepared as reference compounds by a similar N-demethylation-alkylation route from dihydrocodeinone.

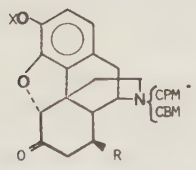
Scheme 2

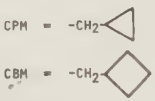


Analgesic data for compounds 8 and 9 are presented in Table 2. The data given are the ED_{50}'s for analgesia in the mouse writhing assay (Whittle 1964) and for narcotic antagonism against morphine in the rat tail flick test (Harris and Pierson 1964). Also included are the agonist-antagonist ratios (MW/AD). Numbers in this column greater than 1 indicate the compound is more antagonistic than analgesic while ratios less than 1 indicate compounds which are more analgesic. In general, N-cyclopropylmethyl (CPM) compounds are strong antagonists while the N-cyclobutylmethyl (CBM) compounds are more analgesic.

Table 2

ED_{50} (mg/kg)





MW - ANALGESIA, MOUSE WRITHING

AD - MORPHINE ANTAGONISM, RAT

8 X = CH_3

9 X = H

		CPM			CBM		
	R	MW	AD	MW/AD	MW	AD	MW/AD
8	H	17.0	3.4	5.0	8.8	IA/3.0	-
	Me	13.0	7.1	1.8	4.5	9.7	.46
	Et	2.1	0.78	2.7	9.6	IA/3.0	-
	Pr	26.0	14.1	1.8			
9	H	1.34	0.19	7.1	0.07	1.7	.04
	Me	> 10	2.3	-	0.67	1.9	.35
	Et	7.8	0.25	31.	9.2	0.52	17.

In the 3-methoxy series 8 CPM, the 8β-alkyl substituent has the effect of increasing the potency of both the analgesic and antagonist activities for R equal methyl or ethyl. As seen with the agonists 2, the potency drops off sharply when R is propyl. We therefore did not prepare any other antagonists where R is other than methyl or ethyl. For the 3-hydroxy series, 9 CPM, the 8β-methyl group decreases the analgesic potency over the reference 8-hydrogen compound. The 8β-ethyl group restores antagonist potency but without a similar increase in analgesia.

In the 3-methoxy-N-cyclobutylmethyl series 8 CBM, the effect of 8-substitution is unpredictable. None of the compounds are, however, of sufficient potency to warrant further investigation. The introduction of an 8β-alkyl substituent in the corresponding 3-hydroxy series 9 CBM at first results in a decrease in analgesia while retaining antagonist potency. The 8β-ethyl function further decreases the analgesic activity while boosting the antagonist potency by a moderate amount.

314-300 O -80 - 8

On the basis of potency considerations, the 3-methoxy-8β-ethyl CPM and 3-hydroxy-8β-methyl CBM compounds have been studied further in other pharmacological models. The pharmacological properties of the 3-methoxy-8β-ethyl CPM compound, TR-5109, are the subject of another presentation at this meeting (Howes et al. This volume).

To summarize, we have shown that introduction of a small alkyl group in the β position at C-8 can affect the agonist to antagonist ratios of N-substituted dihydrocodeinones and dihydromorphinones. The activity of these novel compounds is clearly dependent on both the 8-alkyl and nitrogen substituents. In addition to further pharmacological studies with 17-cyclopropylmethyl-8β-ethyl-7,8-dihydronorcodeinone (TR-5109), we have also extended this work to the morphinan-6-one series. This continuing work will form the basis of future communications from these laboratories.

This study has led to the synthesis of a novel analgesic narcotic antagonist. But, have we succeeded in our goal of utilizing the proposed lipophilic area on the opiate receptor? The compounds prepared in this study do not have analgesic potency in the range of ring C bridge tetrahydro-oripavines. We have, however, found a site which does modify the narcotic agonist-narcotic antagonist profiles of opiate derivatives. We have succeeded in the practical goal of obtaining a useful analgesic agent - TR-5109.

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The Pharmacology of TR5109, a New Narcotic Agonist/Antagonist Analgesic

Howes, J. F.; Osgood, P. F.; Razdan, R. K.; Moreno, F.; Castro, A.; and Villareal, J.

The search for a reliable analgesic without physical dependence liability led to the development of the narcotic agonist antagonist analgesics. While these compounds are not without problems, useful analgesic activity has been obtained. Pentazocine (Talwin) is the most successful compound of this series to date.

The criteria desirable for a compound in this series are that it should be reasonably potent with good narcotic antagonist activity. The compound should not cause constipation and should be free of dependence liability.

METHODS

a) Mouse Acetic Acid Writhing Test

Male albino CD-1 mice (18-22 g) were used for this study. A modification of the Whittle (1964) procedure was used. The test drug was given by subcutaneous injection 15 minutes prior to an intraperitoneal injection of 0.5% acetic acid (0.4 ml). The number of writhes per group of five mice were counted for 20 minutes starting five minutes after the acetic acid injection. Analgesic potency was calculated from the difference between the test groups and their controls.

b) Rat Tail-flick Procedure (for Narcotic Antagonist Activity)

Male Albino Wistar rats (100-150 g) were used for this study. The method described by Harris and Pierson (1964) was used.

Two control reaction times were determined thirty minutes apart and prior to intraperitoneal injection of the test drug. Ten minutes later an ED_{80} dose of morphine was administered subcutaneously and reaction times were then determined twenty minutes later. The narcotic antagonist activity was determined from the difference between the groups and control groups which received morphine alone.

c) Estimation of Physical Dependence Liability in the Rat

The method described by Teiger (1974) was used. Male Albino Wistar rats (200-240 g) were implanted with a polyethylene cannula from the peritoneal cavity, and subcutaneously to an exit between the ears.

This cannula was connected to an infusion pump via a swivel arrangement which allows the animal freedom of movement. Morphine or the test drug was infused for six days (see Table 3 for schedule). At the end of 6 days the infusion was stopped and symptoms of withdrawal were observed for up to 96 hours.

In some experiments at the end of a six-day morphine infusion a 24-hour infusion of the test drug was substituted. The animals were observed for signs of withdrawal during this 24-hour period and for a further 48 hours.

d) Mouse Charcoal Meal Test
The method of Rodriquez and Villarreal (1974) was used. Mice were given a bolus of charcoal and tragacanth 15 minutes after a dose of the test drug. 15 minutes later the animals were sacrificed and the distance that the bolus had travelled along the gastro-intestinal tract was determined.

Inhibition of gastro-intestinal motility was determined by comparison with untreated animals.

e) Guinea Pig Ileum
Guinea pig ilea were dissected according to the method of Kosterlitz and Watt (1968). The segments were incubated overnight in a medium containing the test drug.

The following day these segments were challenged with a dose of naloxone (300 nM). The spontaneous contraction induced by naloxone was measured.

f) Respiratory Depressant Studies
Male Wistar rats (300-500 g) were anesthetized with sodium pentobarbital (50 mg/kg ip) and placed on a warming plate. Rectal temperature was monitored and maintained at 37° throughout the experiment. An external jugular vein and a carotid artery were cannulated. A tracheotomy was made and a short cannula was inserted.

The following variables were measured using a Grass polygraph: Mean arterial blood pressure, ECG, heart rate, tidal volume, respiratory rate and minute volume.

RESULTS
TR5109 was selected from a series of 8β ethyl dihydrocodeinones and dihydromorphinones, based on its pharmacological profile (See Table 1). TR5109 had the best combination of narcotic agonist and antagonist activities in this series.

TR5109 had a duration of action in rodents similar to pentazocine and produced no overt symptomology in rodents at doses well above the analgesic dose.

TR5109 did not cause severe effects on gastro-intestinal motility. TR5109 was similar to pentazocine in this preparation. Its effects were at doses well above the analgesic doses. (Table 2).

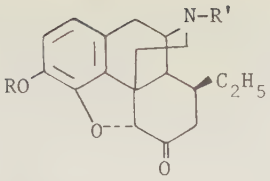

Table 1 - Analgesic and narcotic antagonist activities of 8β ethyl dihydrocodeinone and dihydromorphinones.

#	R	R'	ED_{50} Mouse Writhing (mg/kg, sc)	AD_{50} Rat Tail Flick (mg/kg, ip)
I TR5109	CH_3	$-CH_2$-cyclopropyl	2.1 (0.3 - 13.6)[a]	0.78 (0.31 - 1.96)
II	H	$-CH_2$-cyclopropyl	7.8 (4.4 - 13.9)	0.25 (0.08 - 0.80)
III	CH_3	$-CH_2$-cyclobutyl	9.6 (3.7 - 24.6)	Ia[b] @ 3.0
IV	H	$-CH_2$-cyclobutyl	9.2 (2.5 - 33.9)	0.52 (0.18 - 1.53)
V	CH_3	$-CH_2$ $CH=CH_2$	> 10.0	5.6 (1.9 - 17.0)
VI	H	$-CH_2$ $CH=CH_2$	Ia @ 10.0	0.58 (0.05 - 6.6)
VII	CH_3	$-CH_2$-furan	>10.0	> 10.0
VIII	H	$-CH_2$-furan	1.06 (0.25 - 4.54)	1.80 (1.24 - 2.62
	Pentazocine		3.7 (2.45 - 5.50)	10.4 (3.9 - 28.7)
	Cyclazocine		0.11 (0.03 - 0.45)	0.22 (0.13 - 0.39)
	Morphine		0.79 (0.42 - 1.5)	-
	Codeine		4.2 (1.1 - 16.2)	-

[a] 95% Confidence limits

[b] Inactive

Table 2 - Inhibition of gastrointestinal motility in mice

Compound	Maximum Inhibition	Dose for Maximum (mg/kg, sc)	Dose for 1/2 Maximum (mg/kg, sc)
TR5109	67%	100.0	10.0
Pentazocine	71%	100.0	10.0
Morphine	100%	10.0	1.0
Cyclazocine	39%	3.0	0.1

Table 3 - Physical Dependence Liability Study - Weight Changes

Drug	Infusion Schedule	R	% Change in Weight from Day 0[a] on Day +1	Day +2	Day +3	Day +4
Morphine	50 mg/kg/day for 1 day 100 mg/kg/day for 1 day 200 mg/kg/day for 4 days	8	-16.8* ± 1.3	-12.7* ±1.9	- 7.8* ± 2.3	- 1.6 ± 4.6
Pentazocine	200 mg/kg for 6 days	4	- 7.7* ± 3.9	+ 3.6 ± 2.7	+ 3.7 ± 5.0	+ 3.8 ± 6.5
TR5109	200 mg/kg for 6 days	6	+ 5.1 ± 2.5	+ 4.9 ± 4.8	+11.9 ± 4.3	+13.6 ± 7.3
TR5109	400 mg/kg for 6 days	2	- 0.5	+ 3.8	+ 9.7	+11.5
Control	Saline for 6 days	8	+ 2.7 ± 1.5	+ 7.1 ± 1.51	+ 8.8 ± 2.2	+ 9.6 ± 3.8

[a]Cessation of Infusion

*$P < 0.05$

Table 4 - Induction of Withdrawal Signs by TR5109 and Naloxone in Morphine-Dependent Rats

Symptom	TR5109 (10.0 mg/kg ip)	Naloxone (2.0 mg/kg ip)	Saline
Teeth Chattering[a]	1.17 ± 0.17	3.20 ± 1.01	0.00
Tremors[a]	8.67 ± 0.99	7.20 ± 1.61	0.00
Chewing[a]	8.17 ± 0.31	3.40 ± 1.12	0.00
Wet dog shakes[b]	15.50 ± 3.87	8.20 ± 2.67	0.00
Irritability[c]	6/6	5/5	1/5
Aggression[c]	3/6	1/5	0/5
Vocalization[c]	4/6	1/5	1/5
Diarrhea[c]	2/6	3/5	1/5
4 hr Weight loss (%)	7.67 ± 1.38	6.22 ± 1.01	2.14 ± 0.71

[a]Mean number of 3 minute periods/hour that animals showed response

[b]Mean number of wet dog shakes per hour

[c]Ratio of animals showing responses at 1 hour

[d]Expressed as mean % loss at 4 hours

Table 5 - Guinea Pig Ileum Data

Compound Incubated with Ileum	Response in GMS (Tension) to Naloxone (300 nM)
Levorphanol (64 nM)	2.80 ± 0.40
Morphine (480 nM)	2.42 ± 0.07
Pentazocine (1715 nM)	0.43 ± 0.02
Nalorphine (156 nM)	0.64 ± 0.10
Cyclazocine (24 nM)	0.27 ± 0.07
TR5109 (480 nM)	0.44 ± 0.30
Fresh Ilea	0.71 ± 0.18

Table 6 - The effects of intravenously injected TR5109 on the respiration of the anesthetized normotensive rat

	Dose mg/kg	No. Rats		Minutes after Injection 0	5	30
Respiratory Rate (per minute)	1.0	5		100 ±9.6	88 ±7.2	104 ±10.8
			%Δ		-12	+4
	5.0	5		105 ±3.2	94 ±9.2	101 ±3.7
			%Δ		-10	-4
	10.0	5		97 ±9.7	86 ±8.1	94 ±12.5
			%Δ		-11	-3
	40.0	5		104 ±10.9	79 ±7.7	110 ±12.4
			%Δ		-24	+6
				0	10	30
Tidal Volume (me)	1.0	5		1.89 ±0.138	2.02 ±0.240	1.82 ±0.251
			%Δ		+7	-4
	5.0	5		1.93 ±0.065	2.02 ±0.207	1.82 ±0.099
			%Δ		+13	+5
	10.0	5		1.88 ±0.199	2.65 ±0.840	2.26 ±0.497
			%Δ		+41	+20
	40.0	5[a]		1.90 ±0.146	2.09 ±0.328	1.85 ±0.295
			%Δ		+10	-3
				0	5	30
Minute Volume (me/min)	1.0	5		200 ±23.2	181 ±24.4	207 ±36.7
			%Δ		-10	+4
	5.0	5		220 ±26.7	209 ±35.6	216 ±31.6
			%Δ		-5	-2
	10.0	5		182 ±24.6	247[b] ±92.3	229 ±72.8
			%Δ		+36	+26
	40.0	5[a]		191 ±15.5	161 ±24.5	191 ±24.5
			%Δ		-16	0

[a] 2 other rats died shortly after this dose was injected

[b] Effect at 10 minutes. Minute volume was consistently elevated at this dose (10.0 mg/kg) with the maximum increase occurring at 10 minutes.

Using the rat infusion procedure TR5109 was shown not to produce physical dependence in rodents. At the termination of the procedure TR5109 showed no symptoms of withdrawal and weight changes were not significantly different from controls (Table 3). This was in marked contrast with pentazocine which caused a significant weight loss and other signs of withdrawal following termination of infusion. TR5109 did not substitute for morphine in this procedure and appeared to exacerbate the withdrawal (Table 4). Further, in physically dependent monkeys TR5109 did not support morphine addiction (A. Jacobson-personal communication).

Incubation of TR5109 with guinea pig ilea did not induce a state of physical dependence as defined by the subsequent response to a test dose of naloxone. The results are presented in Table 5.

The response to a test dose of naloxone was smaller after incubation with TR5109 than with pentazocine.

TR5109 had no significant effects on the cardiovascular system of the dog nor did it cause any respiratory depressant effects in the rat (Table 6).

CONCLUSIONS

TR5109 represents a logical chemical modification of established analgesic structures to yield an interesting compound. TR5109 shows analgesic activity in animals in the same ranges as both morphine and pentazocine. It is a more potent narcotic antagonist than pentazocine. TR5109 is similar to pentazocine in mouse charcoal meal test. The rat infusion procedure and the guinea pig ileum data indicate that TR5109 is superior to pentazocine, TR5109 causing no "physical dependence" in the rat and a much smaller effect on the guinea pig ileum preparation.

TR5109 is free of cardiovascular and respiratory depressant effects in animals.

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Dependence Potential of Loperamide Studied in Rhesus Monkeys

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Loperamide is an antidiarrhetic similar to diphenoxylate that has been recently developed by Janssen Pharmaceutical Co. It is water soluble up to only 0.1 percent at room temperature. The pharmacodynamic profile of loperamide is similar to that of diphenoxylate (Shoji et al 1978a & 1978b); however it is believed that loperamide has a more potent therapeutic effect with less frequent systemic side effects in humans than diphenoxylate because of its low absorbability from the gastro-intestinal tract. Since diphenoxylate is known to possess a morphine-like dependence potential (Fraser & Isbell 1961), the dependence potential of loperamide was tested by 9 experiments using rhesus monkeys.

METHODS

1. Gross Behavioral Observation of Acute Central Nervous System Effects in Normal Monkeys

Twenty-two normal adult male and female monkeys were housed 4 to 6 monkeys per cage. Single doses of loperamide were administered, and the monkeys' gross behavioral manifestations of drug effects were observed prior to and after administration until the disappearance of the drug effects. Doses used were: 0.25, 0.5 and 1 mg/kg i.v.; 0.25, 1, 4, and 8 mg/kg s.c.; and 0.25, 1, 4, and 16 mg/kg p.o. For i.v. and low-dose s.c. use, the drug was prepared by first dissolving in distilled water and then adjusting the solution to isotonicity with NaCl. For high-dose s.c. and p.o. use, the drug was prepared with a 0.5 percent sodium carboxymethylcellulose-water suspension.

2. Suppression of Withdrawal Signs by Single Dose Administration of Loperamide to Morphine Dependent and Withdrawn Monkeys

Monkeys were made physically dependent by repeated s.c. administration of 3 mg/kg of morphine HCl 4 times daily for longer than 8 weeks. The drug was then withdrawn for about 10 hours and when the animals manifested morphine withdrawal signs, single doses of

loperamide at 0.25, 1, and 4 mg/kg were given s.c. to 2 or 4 monkeys each, with observation for changes in the signs continued for 7 hours. For comparison, saline, morphine HCl at 3 mg/kg, and codeine phosphate at 16 mg/kg were used.

3. Development of Physical Dependence on Loperamide by Repeated Administration to Normal Monkeys

The experiment consisted of 3 parts using different subjects.
Part 1. Subcutaneous administration of loperamide.
Five normal male and female monkeys were administered loperamide s.c. at doses of 1 mg/kg 4 times daily for 31 days. On days 14 and 28 the naloxone precipitation test was conducted by single dose administrations of naloxone HCl at 1 mg/kg s.c. The natural withdrawal test was conducted from day 32 for 5 days. During the administration period, gross behavior was observed regularly with body weights determined weekly. Withdrawal observations were conducted blind and severity of the withdrawal signs were graded according to Seevers' criteria (Seevers 1936).
Part 2. Oral administration of relatively high doses of loperamide.
Five normal male and female monkeys were orally administered loperamide by gavage at a dose of 2 mg/kg twice daily for 31 days. The naloxone tests, natural withdrawal test, and all other observations were conducted as described in part 1.
Part 3. Oral administration of relatively low doses of loperamide.
Based on the fact that the blood level of loperamide in humans reaches 10 ng/ml at the highest even after the maximally ingestable experimental doses (Weintraub et al 1977), the possibility of development of physical dependence on the drug was studied in rhesus monkeys at around these blood levels. Since oral administration of the drug to rhesus monkeys at 2 mg/kg every 12 hours brought their blood level to approximately 100 ng/ml, in this test each dose was 0.2 mg/kg. The experiment was started in 6 normal monkeys following the procedure described above. Two weeks later, the blood levels were determined and it was found that the levels were relatively high (average 15.9 ng/ml) in 3 of the monkeys and low (average 7.2 ng/ml) in the other 3 (Suzuki et al 1978). The low group was continued with the same doses for another 4 weeks and 5 days. The doses for the high group were reduced to 0.05 mg/kg for 2 weeks, and then increased to 2.0 mg/kg for the remaining time up to the 47th day of the experiment. The blood level of the high group was determined again at the end of the 0.05 and 2.0 mg/kg administration periods. All monkeys were subjected to the naloxone test on the 14th, 28th, and 42nd days, and to the natural withdrawal test for 5 days at the end of the 47-day administration period.

4. Intravenous Cross Self-Administration of Loperamide with Lefetamine and Saline

Six monkeys that had been trained by a method described elsewhere (Deneau, Yanagita and Seevers 1969) to intravenously self-administer lefetamine, a standard reinforcing agent, were tested with lefetamine, saline, and loperamide for 3 successive days each, at 4 hours per day using an FR 1 schedule. This procedure was repeated 3 times for 3 unit doses of loperamide: 4, 15, and 60 μg/kg/inj. The

unit dose of lefetamine was always 0.01 mg/kg/inj.

5. Continuous Self-Administration of Loperamide

Part 1. Intravenous self-administration.
Two monkeys that had previous experience with i.v. self-administration of lefetamine were tested for 1 to 2 weeks with i.v. self-administration of saline without time limitations, after which the animals were allowed to self-administer loperamide at a unit dose of 0.06 mg/kg. One week later the unit dose was increased to 0.25 mg/kg. This time a 2-hour time-out was scheduled after every 4 doses taken within 24 hours because in the preceeding study it had been determined that the animals would die if allowed to overdose. When the animals had shown active self-administration of the drug for 3 to 4 days the unit dose was cut back to 0.06 mg/kg, the time-out schedule was cancelled, and the experiment was continued for 4 weeks. Then, after a 2-day withdrawal test, the experiment was continued for another 4 weeks at the same unit dose, and finally a 5-day withdrawal was conducted. Since experienced monkeys were found to be taking the drug in the first test, a further experiment similar to the above was conducted using 2 naive monkeys.
Part 2. Intragastric self-administration.
Four monkeys that had previous experience with i.v. self-administration of pentazocine and/or lefetamine were allowed to intragastricly self-administer loperamide without time or dose limitations at a unit dose of 0.25 mg/kg for 6 weeks, and then at 0.5 mg/kg for the 4 to 6 weeks. After this, all monkeys received programmed intragastric administration of the drug at a dose of 4 mg/kg twice daily for 2 weeks, followed by further observation of intragastric self-administration at 0.5 mg/kg for 2 more weeks, and at 0.125 mg/kg for another 2 weeks. Upon termination of the intragastric experiment, the intravenous experiment was conducted in the same animals at a unit dose of 0.06 mg/kg for 2 weeks.

6. Progressive Ratio Test for Intravenous Self-Administration of Loperamide

Three monkeys that had been trained to self-administer lefetamine i.v. at FR 100 were used in this test. Each trial consisted of 3 periods: a pretreatment period, an FR 100 period, and progressive ratio period. Each monkey successively underwent 6 trials in a counterbalanced design. In the pretreatment period, either loperamide (0.06 mg/kg), codeine phosphate (1 mg/kg), or saline (0.25 ml/kg) was administered i.v. every 20 min, 72 times daily for 7 days. Self-administration was not available in this period. During the FR 100 period the animals were allowed to self-administer the designated agent at the above-indicated unit dose under the FR 100 schedule for 24 hours. In the progressive ratio period the ratio started at 100:1, increasing geometrically by a factor of $\sqrt{2}$ at every dose, and continued until the number of lever presses during 48 hours failed to reach 50 percent of that required for the next dose, upon which the trial was terminated, with the ratio achieved for the last administered dose being regarded as the final ratio. Throughout the experiment each self-administration was followed by a 15 min

time-out period which was indicated to the animal by a panel light.

RESULTS

1. Gross Behavioral Observation of Acute Central Nervous System Effects in Normal Monkeys

The acute CNS effects of loperamide were morphine-like; it produced a decrease in awareness of fellow monkeys and the observers, drowsiness, mydriasis, and skin scratching. These effects were observed at doses higher than 0.25 mg/kg i.v. and 10. mg/kg s.c. or p.o. When 1.0 mg/kg was administered, the approximate times for the onset and duration of drug effects were, respectively: i.v., ¼ and 30 hours; s.c., ½ and 30 hours; and p.o., 1 and 20 hours. The doses of 8 mg/kg s.c. and 16 mg/kg p.o. were toxic with one out of 2 monkeys in each group dying 5 and 4 hours respectively after administration due to respiratory and cardiac failure.

2. Suppression of Withdrawal Signs by Single Dose Administration of Loperamide to Morphine Dependent and Withdrawn Monkeys

All monkeys manifested an intermediate grade of morphine withdrawal signs about 10 hours after the last dose of morphine. Single doses of loperamide did not suppress the withdrawal signs at 0.25 or 1.0, but did so at 4.0 mg/kg s.c. The suppression was complete in 2 of the monkeys and nearly complete in the other 2. Exactly the same results as the above were obtained with morphine at 3.0 mg/kg s.c. Codeine at 16.0 mg/kg s.c. also resulted in nearly complete suppression.

3. Development of Physical Dependence on Loperamide by Repeated Administration to Normal Monkeys

Part 1. Subcutaneous dministration of loperamide.
As the repeated s.c. administration began, drowsiness was observed in all 5 monkeys. The drowsiness weakened gradually in the 3rd and 4th weeks of administration, but motor activity was still slow. The results of the 2 naloxone tests and the natural withdrawal test are shown in Table 1. The development of physical dependence on loperamide was quite evident from these results.

TABLE 1. Development of Physical Dependence by Repeated Subcutaneous Administration of Loperamide

Monkey	Body weight (kg)				Grade of withdrawal signs[c]		
	Initial	14th day	28th day	Withdr. period[b]	Naloxone test (1mg/kg, s.c.)		Withdrawal test[d]
					14th day	28th day	
#613 female	3.6	3.4	3.3	3.2	Severe	Severe	Intermediate
#752 male	3.3	3.2	3.1	3.1	Severe	Severe	Intermediate
#770 male	3.3	3.3	3.4	3.2	Severe	Intermediate	Severe
#771 male	2.9	3.0	2.9	2.8	Severe	Severe	Intermediate
#787 male	3.4	3.4	3.1	2.8	Severe	Severe	Severe

a) Dosing schedule : 1mg/kg, s.c. 4 times daily for 31 days
b) Minimum body weight during a 5-day withdrawal period (32~36 th day)
c) Graded by Seevers' criteria
d) Heaviest grade during the 5-day withdrawal period.

Part 2. Oral administration of relatively high doses of loperamide.
The results of the repeated oral administration experiment were quite similar to those of the s.c. experiment, except that the development of physical dependence appeared to be somewhat slower by this route.

Part 3. Oral administration of relatively low dose of loperamide.
No effect was observable in the monkeys treated with repeated oral administration of loperamide at 0.2 mg/kg twice daily for 2 to 6 weeks. The naloxone test on day 14 did not precipitate any withdrawal signs in any of the 6 monkeys. The administration was further continued at the same dose in half of the monkeys (Group A) still the naloxone tests on days 28 and 42 and the natural withdrawal test from day 48 to 52 failed to show any indication of development of physical dependence. In Group B, definite development of physical dependence was shown by both the naloxone and natural withdrawal tests but only when treated with loperamide at 2.0 mg/kg twice daily for 2 weeks (Table 2).

TABLE 2 Development of Physical Dependence by Small Oral Doses

Group	Monkey	Body weight (kg)					Grade of withdrawal signs[c]			
		Initial	14th day	28th day	42nd day	Withdr. period[b]	Naloxone test (1 mg/kg, s.c.)			Withdrawal test[d]
							14th day	28th day	42nd day	
A	#938 male	5.2	5.2	5.2	5.3	5.3	None	None	None	None
	#945 female	4.3	4.4	4.2	4.5	4.4	None	None	None	None
	#962 female	4.0	4.0	4.2	4.4	4.1	None	None	None	None
B	#931 female	4.2	4.0	4.0	4.1	3.8	None	None	Severe	Intermediate
	#959 male	5.0	5.0	5.2	5.1	4.9	None	None	Intermediate	Intermediate
	#963 female	4.6	4.6	4.8	4.4	4.0	None	None	Intermediate	Intermediate

a) Dosing schedule : Group A-0.2 mg/kg, p.o. twice daily for 47 days.
Group B-Same as Group A for the first 14 days, 0.05 mg/kg twice daily from 15 to 28th day, and 2.0 mg/kg twice daily from 29 to 47th day
b) Minimum body weight during a 5-day withdrawal period (48～52nd day)
c) Graded by Seevers' criteria d) Heaviest grade during the 5-day withdrawal period.

4. Intravenous Cross Self-Administration of Loperamide with Lefetamine and Saline

During the daily 4-hour sessions, frequent intake for lefetamine and infrequent intake for saline were observed in all 6 monkeys (Table 3). The intake ratio of loperamide against the reference drug significantly higher than that of saline at a unit dose of 15 μg/kg.

5. Continuous Self-Administration of Loperamide

Part 1. Intravenous self-administration.
Both experienced and naive monkeys initiated and maintained self-administration when allowed to take the drug at a unit dose of 0.25 mg/kg. Once initiated they maintained this behavior at a unit dose of 0.06 mg/kg (Table 4). The highest daily dose taken by any monkey was 7.05 mg/kg/day in an average over a 2-week period.

TABLE 3 Intravenous Cross Self-Administration of Loperamide with Lefetamine and Saline

Monkey	Average No. of self-administ.	Percent ratio of self-administration rate, lefetamine as 100%			
	Lefetamine	Saline	Loperamide (mg/kg/inj.)		
	0.1mg/kg/inj.	0.25ml/kg/inj.	0.004	0.015	0.06
	(/4hrs/day)	(%)	(%)	(%)	(%)
#648 male 4.1kg	390.5	10.1	53.8	36.6	11.7[b]
#673 male 4.0kg	203.4	6.6	2.5	13.5	38.1
#758 female 4.1kg	193.1	8.9	6.9	40.5	12.6
#768 male 4.3kg	260.9	7.5	5.3	41.8	11.0[c]
#798 male 3.5kg	320.9	6.2	0.3	33.3	8.7[c]
#799 male 3.7kg	213.2	14.4	15.8	37.8	5.2[c]
Mean ± S.D		9.0±3.1	14.1±20.2	33.9±10.5**	

a) *l*-1, 2-diphenyl-dimethyl-aminoethane HCl

b) Overdosed and fell into coma on the 2nd day of the test at this unit dose and the test was terminated. This monkey died 4days later.

c) Self administration was limited to shorter than 4hours for prevention of the overdose.

** $P<0.01$ against saline

In these animals, although CNS depression was observed, no such toxic manifestations as paralysis, coma, respiratory insufficiency, convulsions, or death were observed. In the 2-day withdrawal test conducted at the end of the 4-week self-administration period, all monkeys manifested severe withdrawal signs and increased their lever-pressing responses. This increase was particulary marked in the naive monkeys. Self-administration was resumed in 3 monkeys for an additional 2 to 4 weeks, and a further increase of the daily dose level was observed in 2 of the monkeys. In the 5-day withdrawal test, the withdrawal signs in monkeys #681 were very severe and a gradual withdrawing schedule by programmed administration of loperamide had to be implemented.

Part 2. Intragastric self-administration.

During the 10 to 12-week periods none of the 4 monkeys initiated self-administration of loperamide by the intragastric route at the unit doses of 0.25 or 0.5 mg/kg. Programmed administration of the drug at 4.0 mg/kg twice daily for 2 weeks also failed to result in initiation of self-administration. Therefore the experiment was continued changing to the i.v. route in all except one monkey which died during the programmed administration period. This time all 3 monkeys initiated self-administration.

TABLE 4. Continuous Intravenous Self-Administration of Loperamide

Monkey	Naive or experienced	Average daily number of self-administration						
		Saline 0.25ml/kg/inj. for 1week	Loperamide 0.06mg/kg/inj. for 1week	0.25 for 2-4days[a]	0.06 for 2w×2periods	Withdrawal for 2days	0.06 for 2w×2	Withdrawal for 5days
#669 female 4.3kg	Experienced[b]	0.6	1.0	15.0	44.8, 36.9	(1st d. 120) (2nd d. 46)	38.2, 47.0	(1st d. 232) (2nd d. 234)
#681 male 4.4kg	Experienced[b]	2.3	2.0	7.0	29.9, 47.4	(1st d. 227) (2nd d. 61)	72.7, —	(1st d. 518) (2nd d. 68)
#641 female 4.6kg	Naive	2.7	—	4.8	35.6, 117.5	(1st d. 405) (2nd d. 42)	— —	—
#779 male 3.2kg	Naive	2.7	—	6.0	36.0, 65.0	(1st d. 493) (2nd d. 139)	86.7, —	(1st d. 453) (2nd d. 108)

a) Deprived for 2hours after every four intakes. The period before initiation of self-administration not included.

b) Previously experienced with intravenous self-administration of lefetamine but deprived from any experiments for longer than 1month.

6. Progressive Ratio Test for Intravenous Self-administration of Loperamide

In the first trial for saline the monkeys only took a few doses during the FR and PR periods, with the final ratios recorded as 140, 120, and 170 in monkeys #325, 478, and 769, respectively (Table 5). In the trials for codeine, the number of self-administrations in 2 monkeys was fewer when pretreated than when not pretreated for all 3 monkeys (Table 6). In the trials for loperamide, the number of self-administrations during the FR and PR periods tended to be lower than was the case for codeine regardless of whether or not the animals were pretreated. The final ratio was also generally low, particularly in monkeys #325 and 769 when pretreated. When pretreated with codeine or loperamide, mild to intermediate grades of withdrawal signs were observed during the FR and/or PR periods.

TABLE 5 Final Ratios in the Progressive Ratio Test

Monkey	Saline	Codeine phosphate		Loperamide HCl		Saline
		1.0 mg/kg/inj.		0.06 mg/kg/inj.		
	0.25 ml /kg/inj.	Pretreated with codeine[a]	Control (saline)	Pretreated with loperamide[a]	Control (saline)	0.25 ml /kg/inj.
#325 female 3.6 kg	140 (1)	3200 (2)	2690 (3)	140 (5)	670 (4)	Died (6)
#478 female 3.65 kg	120 (1)	12800 (3)	6400 (2)	1350 (4)	670 (5)	170 (6)
#769 male 4.85 kg	170 (1)	10760 (4)	4530 (5)	0 (3)	570 (2)	340 (6)

a) Pretreated by programmed intravenous administration of the drug at the indicated unit doses every 20 minutes (72 injections/day) for 7 days.

( ) : Test order of trials in each monkey.

TABLE 6 Number of Self-administration in the Progressive Ratio Test

Monkey	Agent	Saline	Codeine phosphate		Loperamide HCl		Saline
	Unit dose (mg/kg/inj.,i.v.)	0.25 ml	1.0		0.06		0.25 ml
			Pretreated	Non-pretreated	Pretreated	Non-pretreated	
No. 325 female 3.6 kg	FR period[a]	4 (1)	0 (2)	53 (3)	7 (5)	16 (4)	Died (6)
	PR period[b]	3	21	20	3	12	–
No. 478 female 3.65 kg	FR	4 (1)	80 (3)	64 (2)	12 (4)	25 (5)	8 (6)
	PR	2	29	25	16	12	4
No. 769 male 4.85 kg	FR	6 (1)	1 (4)	19 (5)	0 (3)	3 (2)	4 (6)
	PR	4	28	23	0	11	8

a) The 24-hour fixed ratio 100 period.

b) The progressive ratio period.

( ) : Test order of trials in each monkey.

DISCUSSION

The pharmacological profile of loperamide observed in this study was very similar to that of morphine or the many morphine-like narcotics in such aspects as the acute CNS effects, the tolerance-and physical dependence-producing properties, antagonization by naloxone, and the positive reinforcing effect of i.v. self-administration. However, loperamide differed from morphine-like narcotics in that it failed to produce physical dependence at oral doses of one-tenth the maximum tolerable dose, it showed no reinforcing effect with the intragastric route of self-administration, and the intensity of its i.v. reinforcing effect as assessed by the progressive ratio test was substantially

weaker than that of codeine even after the development of physical dependence prior to the test. Based on these findings and taking the dose-blood level relationships of rhesus monkeys and humans into account, it was concluded that the development of dependence on this drug is unlikely to occur in humans because the low water-solubility and oral bioavailability may be self-limiting so that any use of the drug will still fail to increase the blood level to the point that dependence may be developed.

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Opioid Self-Administration and REM Sleep EEG Power Spectra

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INTRODUCTION

An animal model of self-maintained drug dependence became available in 1961 when a technique was established which permitted a rat to press a lever switch in order to self-administer morphine, via an indwelling intravenous (iv) cannula (Weeks, 1961); and in this way, the rat resembled a drug addict by maintaining itself in a state of dependence. Meanwhile, studies of the electroencephalogram (EEG) had demonstrated that various states of consciousness such as wakefulness, drowsiness, or sleep were associated with distinct EEG patterns (Morruzzi and Magoun, 1949). Thus, the experimental self-administration model of Weeks was incorporated with a method for chronic recording of cortical EEG (Khazan, Weeks and Schroeder, 1967; Khazan and Weeks, 1968). The resulting experimental model allows continuous recording of ongoing EEG changes during morphine self-administration and provides a basic model for simultaneous study of behavioral and electrophysiological correlates during self-maintained dependence in the rat (see review, Khazan, 1975).

Self-injections of morphine in dependent rats produced a biphasic response consisting of a brief episode of behavioral stupor with EEG slow bursts that was followed by behavioral and EEG arousal (Khazan et al, 1967; Khazan and Weeks, 1968). Sleep and REM sleep episodes then predominated until immediately before the next self-injection. These morphine-dependent rats with free access to an operant lever for self-administration usually took single iv injections (10 mg/kg) every 2 to 3 hours (Weeks and Collins, 1968; Moreton, Roehrs and Khazan, 1976).

We have used this experimental self-administration model to study electrophysiological and behavioral correlates during the self-administration of other narcotics such as methadone, ℓ-alpha-acetylmethadol (LAAM), nor-LAAM (NLAAM), and dinor-LAAM (DNLAAM) (Moreton et al, 1976; Young, Steinfels and Khazan, in press). Although the average intervals between methadone self-injections were shorter than those with morphine (1.5 to 2 hours), similar

biphasic EEG and behavioral responses were seen. Unlike morphine or methadone, however, after LAAM self-injections a few sleep and rapid eye movement (REM) sleep episodes did sometimes emerge before the stuporous phase. Self-administration of NLAAM also produced a biphasic EEG and behavioral response similar to that seen with morphine and methadone. In contrast, there were no apparent relationships between DNLAAM self-injections and distribution of sleep-awake activity.

Recently, power spectral analysis has been used in our laboratory to quantitate EEG parameters not readily discernible by visual observations. The EEG recordings during the three behavioral states of wakefulness, sleep, and REM sleep in the rat demonstrated characteristic power spectra (Young, Steinfels, Khazan and Glaser, 1978a). We have recently found that as time progressed from one morphine self-injection in a dependent rat toward the next injection a significant spectral shift of the EEG to slower frequencies occurred during successive REM sleep episodes (Young, Steinfels, Khazan, and Glaser, 1978). Each morphine self-injection reinstated the predominance of faster frequencies in the REM sleep EEG spectra. We have also found similar changes in EEG frequency during methadone self-administration in the rat (Steinfels, Young, and Khazan, 1978). In the present study we report on comparative changes in EEG power spectra derived from successive REM sleep EEG episodes during self-administration of five narcotics: morphine, methadone, LAAM, and the two active N-demethylated metabolites of LAAM, NLAAM and DNLAAM.

METHODS

Animals and Experimental Preparation

Eighteen adult female Sprague-Dawley rats weighing 250-275 grams were prepared with chronic EEG and EMG (electromyographic) electrodes (Khazan, 1975). Stainless steel screws served as bipolar cortical electrodes and were implanted over the frontal and ipsilateral parietal cortices. For EMG recordings, stainless steel wires were sewn into the left and right temporalis muscles. Wire leads from the EEG and EMG electrodes were soldered into a miniature connector which was secured to the skull with dental acrylic. For drug administration a silicone rubber cannula was implanted in the right jugular vein (Weeks, 1972).

During the experimental procedures, all animals were housed in individual chambers. To permit unrestrained movement of the rat during EEG and EMG recordings, each cage was equipped with a swivel connector with concentric mercury pools which served as noise-free sliding contacts. A feed-through cannula for drug administration extended through the center of each swivel. An eight-hour lights-off period was maintained from 10 p.m. to 6 a.m., and room temperature was kept at 72-78°F.

Drugs Used

The drugs used were: morphine sulfate (Mallinckrodt, Inc., St. Louis, MO.), methadone HCl (Eli Lilly and Co., Indianapolis, IN.), ℓ-alpha-acetylmethadol HCl (NIDA, Bethesda, MD.), noracetylmethadol HCl (NIDA, Bethesda, MD.), and dinoracetylmethadol (NIDA, Bethesda, MD.). All drugs were dissolved in isotonic saline (0.9%) and doses are expressed as the salt. A 0.1 ml volume administered over 6 seconds was utilized during intravenous drug administration.

Drug Self-Administration

Rats were first made tolerant to and physically dependent on morphine by a series of electronically-controlled automatic hourly iv injections. During the first day rats received 1.25 mg/kg/hr of morphine. The dose was increased to 2.5, 5.0, 10.0, and 20.0 mg/kg/hr on successive days. Fifteen of the rats were then trained to lever press on a fixed ratio (FR) schedule of reinforcement to receive morphine (10 mg/kg/injection). An FR of one lever press was initially required per injection, which was gradually increased to FR-20. After one week of stabilized responding for morphine, the rats were divided into five groups of three rats each. One group continued to self-administer morphine. In each of the other four groups, methadone (2 mg/kg/injection), LAAM (1 mg/kg/injection), NLAAM (1 mg/kg/injection), or DNLAAM (1 mg/kg/injection) was substituted for morphine. These doses were selected based upon previous dose-response studies in our laboratory (Moreton et al., 1976; Young et al., in press). At least one week was allowed for restabilization of self-administration patterns and then data were collected for further analysis. The remaining morphine-tolerant rats were not trained to lever press but were given automatic morphine injections every 2.5 hours for at least one week. This interinjection interval of 2.5 hours approximated the average interinjection interval reported earlier during morphine self-administration (Khazan and Weeks, 1968; Moreton et al., 1976).

Data Collection and Analysis of REM Sleep EEG

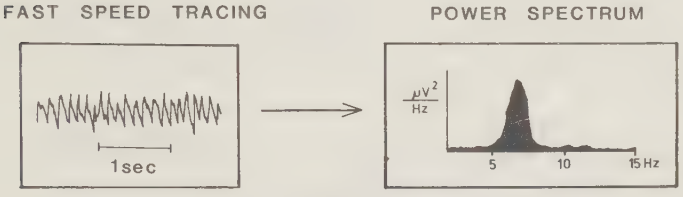
Continuous EEG and EMG activities were recorded on a Grass model 7D polygraph. The EEG was filtered to pass frequencies between 1 and 35 Hz. The EEG activity was also recorded on FM tape with a Hewlett-Packard model 3960-A recorder.

REM sleep onset was determined by the corresponding changes in gross behavior and the appearance of theta waves with a coincident drop in integrated EMG activity (Khazan et al., 1967; Khazan and Weeks, 1968; Khazan, 1975; Moreton et al., 1976). The EEG of the successive REM sleep episodes occurring between drug interinjections were analyzed as follows. Using a Nicolet MED-80 system, power spectra were derived from the EEG during each REM sleep episode. The EEG was digitized at a sampling rate of 54 samples per second, and power spectral densities from zero to 27 Hz were estimated at 0.1 Hz intervals and weighted geometric smoothing over three neighboring frequencies was used.

RESULTS

Figure 1 shows a sample of theta waves recorded during a REM sleep episode. The resulting power spectrum from an entire REM sleep episode is shown on the right. It can be seen that the majority of the spectral power occurred between 5 and 9 Hz (theta band).

FIGURE 1

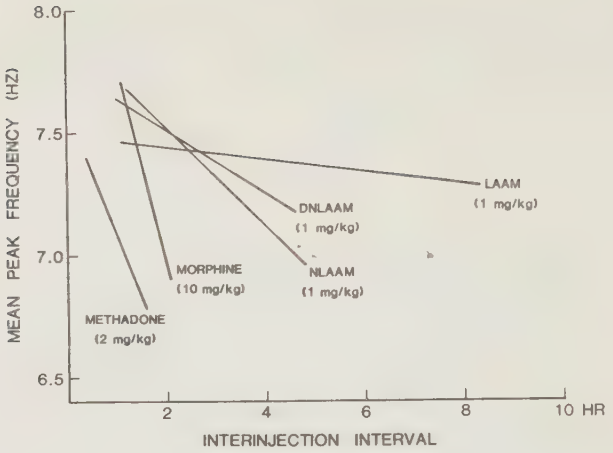


Fast-speed tracing of EEG theta waves during REM sleep in a naive rat is displayed in the left-hand box. A power spectrum derived from REM sleep EEG is shown in the right-hand box. In this example, the majority of the spectral power is in the 5-9 Hz bandwidth and the peak EEG frequency is 7.2 Hz.

Changes in peak EEG frequencies of REM sleep episodes during self-administration of morphine, methadone, LAAM, NLAAM, and DNLAAM are shown in Figure 2 as best-fit linear regression lines. The length of each regression line relative to the x-axis reflects the average duration of the interinjection intervals for that narcotic. Analyses of variance (all $p < .05$) indicated that the changes in mean peak EEG frequencies during morphine [$F(5,10)=17.97$], methadone [$F(7,14)=12.59$], LAAM [$F(8,16=6.82$], NLAAM [$F(7,14)=21.72$], and DNLAAM [$F(9,18=13.64$] interinjection intervals were significant. Analyses of the same data for linear trends were also significant. When the data for all five narcotics were compared in an analyses of covariance, significance was found [$F(5,35=8.65$]. Further analyses of covariance indicated that the linear regressions associated with morphine and methadone were not different from one another, but were different from those associated with LAAM, NLAAM, and DNLAAM. Furthermore, the linear regressions associated with LAAM, NLAAM, and DNLAAM were all significantly different from one another.

In order to determine whether lever pressing activity per se was a significant factor in producing the changes in mean peak EEG frequencies, morphine-tolerant rats were studied while receiving automatically delivered morphine injections. The results were analogous to those obtained during morphine self-administration. As time progressed from one automatic morphine injection toward another injection, a linear decline in mean peak EEG frequencies occurred during successive REM sleep episodes.

FIGURE 2



Mean EEG peak frequencies (Hz) of successive REM sleep episodes during narcotic interinjection intervals are shown as best-fit regression lines. The length of each line relative to the x-axis indicates the average duration between self-injections of the respective drug (interinjection interval). The slopes of the linear regression lines expressed in Hz/hour ± s.d. are: morphine (.72 ± .25), methadone (.53 ± .35), LAAM (.03 ± .02), NLAAM (.21 ± .04), and DNLAAM (.11 ± .07).

DISCUSSION

In a previous report from this laboratory we compared the EEG frequency spectra derived from the first REM sleep EEG episodes after self-injections of morphine in dependent rats with those derived from the last REM sleep episodes just prior to the next injections (Young et al., 1978b). It was found that the average mean peak frequency associated with the first REM sleep EEG episodes was significantly faster than that during the last REM sleep episodes. The present study has extended those findings by demonstrating the existence of linear declines in REM sleep EEG peak frequencies during morphine, methadone, LAAM, NLAAM, and DNLAAM self-administration in dependent rats.

The differences seen in linear regression slopes among the five narcotic drugs (Figure 2) were probably related to differences in their pharmacodynamic properties. Compared to morphine or methadone, LAAM's longer duration of action has been postulated to result from the formation of its active N-demethylated metabolites, NLAAM and DNLAAM. Evidence for this arises from the fact that its two N-demethylated metabolites have been shown to accumulate in the

plasma (Billings, McMahon, and Blake, 1974; Henderson, Weinberg, Hargreaves, Lau, Tyler, and Baker, 1977a; Henderson, Wilson, and Lau, 1977b), and to have relatively long plasma half-lives (Kaiko and Inturrisi, 1975). Therefore, in the present study the smaller slopes of LAAM, NLAAM, and DNLAAM, compared to morphine and methadone, are presumably related to their longer half-lives.

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Motor Activity and Learning Ability in Rats Perinatally Exposed to Methadone

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INTRODUCTION

Methadone is a synthetic narcotic analgesic that is commonly utilized in detoxification and maintenance programs for narcotic-addicted pregnant women (Blinick et al. 1976). In spite of its widespread clinical use, the short-term and long-term consequences of methadone exposure on perinatal development have not been elucidated. However, in the limited number of clinical studies that have been conducted, children delivered by methadone-exposed mothers have been reported to be retarded in body growth (Ting, Keller, and Finnegan 1975; Wilson 1975) and to exhibit behavioral abnormalities (Ting, Keller, and Finnegan 1975).

The developing nervous system of laboratory animals appears to be particularly sensitive to methadone. Previous studies (McLaughlin, Zagon, and White 1978; Thompson, Zagon, and McLaughlin 1979; Zagon and McLaughlin 1977a; 1977b; 1977c; 1978a; 1978b) in our laboratory, using different schedules of maternal methadone treatments, reveal that drug-exposed rat offspring have morphological and biochemical alterations in brain and cerebellar development as well as disturbances in somatic growth and preweaning behavior. The present investigation was undertaken in order to determine the effects of perinatal methadone exposure on motor activity in young rats and to establish whether adult learning ability is impaired.

METHOD

Subjects and Drug Treatment:

Female (180-200 g) and male (250-300 g) Sprague-Dawley rats (Charles River Labs, Wilmington, MA) were utilized in this study and housed under controlled conditions (Zagon and McLaughlin 1977b). Females were treated daily with an i.p. injection of either 5.0 mg/kg dl-methadone hydrochloride (Dolophine), or an equivalent volume of saline. Five days after initiating drug treatment, females were mated. Within 4 hr of birth, 4 groups of animals based on treatment schedule (i.e. exposure to methadone during gestation,

lactation, or gestation-lactation, as well as controls) were established (Zagon and McLaughlin 1977b; 1977c; 1978a; 1978b). All offspring were weighed at birth and on days 21, 45, 60, and 120.

Eight males and 8 females from each of the 4 treatment schedules were tested for activity levels at 21 days of age, and 4 males and 4 females from each group were tested at 45 and 60 days. At 120 days, 6-9 female rats comprised each of the treatment groups.

Apparatus and Procedures:

Activity cage. A cylindrical activity cage (Lehigh Valley Electronics, Model 145-03), 60 cm in diameter and 38 cm high, which contained 6 banks of infrared photobeams was utilized to assess locomotor activity in a darkened area. An animal's movement was measured as the total number of photobeam interruptions during a 5 min period.

Open field. The open field was constructed of masonite with a 52.5 cm x 52.2 cm surface divided by painted lines into 25 squares; the walls were 20 cm high. Illumination was provided by standard fluorescent ceiling lights and all lights were turned on throughout the test period. During testing each rat was placed in the center square of the field and allowed to explore the area for 5 min. Locomotion was scored as the total number of squares entered with all four paws.

Animals were tested at three age periods: days 21, 45, and 60. On day 21, rats were removed from their home cages, marked for identification, placed in plastic holding cages (5 rats per cage), and allowed one hr to acclimate to the testing location. Each test required approximately 5 min, with a minimum interval of 50 min between tests. Test order was randomized for all animals in order to control for effects of order of presentation. Rats were returned to their home cages at the end of each test day. This procedure was replicated at each age.

Active avoidance. The apparatus for conducting active avoidance tests was a standard 2-way shuttle box (Lafayette Instrument Co.). A 6 W light bulb, suspended from the ceiling, was used as the conditioned stimulus and a 1 ma shock passed through a Lehigh Valley model 1531 scrambler was the unconditioned stimulus.

Tests were designed to measure the ability of an animal to respond to a visual signal within 5 sec by crossing a barrier in order to avoid receiving a footshock. On day 1, rats were habituated to the shuttle box for a 15 min period. On each of the next 5 days, 20 avoidance training trials (total 100 trials) with 45 sec intertrial intervals were conducted. Illumination of the test compartment signalled that shock would be administered in 5 sec. If the rat crossed to the alternate compartment within this interval, no footshock occurred and an avoidance response was recorded. If an avoidance was not made, a 1 ma footshock was administered and terminated when the animal crossed to the other compartment (escape).

Footshock was terminated and the trial ended if the rat did not successfully cross to the other compartment within 10 sec.

Discrimination learning. Animals were tested in a 4-unit discrimination box (Krechevsky 1932). Rats were habituated by allowing them to freely explore the discrimination apparatus for 15-min sessions on each of 5 days. During the entire testing period, rats were maintained on a one hr per day feeding schedule, with food available for one hour immediately following each test session; a palatable wet mash was also present in the goal box. During actual training, one randomly chosen alleyway was illuminated and a barrier was positioned across the darkened exit on the opposite side. The rat was placed in the start box and allowed to find its way to the goal box. The guillotine doors of each compartment were lowered after the animal passed into the next compartment in order to prevent the rat from returning to the start box. Each rat made 5 runs (20 discriminations) per day for 5 days; a one-minute interval in the goal box was allowed between runs. A wrong choice was recorded if the rat's head and forefeet passed through the opening of a blocked alley. The sequence of lighted and darkened choice-points was randomized for each of the 25 runs.

Data analysis. Body weights were evaluated by analysis of variance with Treatment Schedule and Sex considered as between-groups variables and Age as a repeated measure; subsequent analyses were made using Dunnett's procedure (Winer 1971).

Performance on each of the activity measures was evaluated by analysis of variance. At 21 days, two-factor analyses of variance were used to evaluate the number of squares entered in the open field and number of photobeam interruptions in the darkened activity cage. Sex and Treatment Schedule were treated as between-groups variables. Because group size differed, data obtained at 45 and 60 days were evaluated using a three-factor analysis of variance with Sex and Treatment Schedule as between-groups variables and Age (45 or 60 days) as a within-groups variable. Subsequent comparisons involving groups were made using Dunnett's procedure (Winer 1955).

RESULTS

Body Weights:

Rats that were perinatally exposed to methadone tended to weigh less than controls prior to sexual maturity, but differences were reliable only at certain ages for males. Males exposed to methadone during lactation weighed less than controls at 45 and 60 days of age, and those exposed to drug only during gestation had body weights that were less than controls at 60 days. Body weights of animals in the gestation-lactation group did not differ from controls at any age. By 120 days, female rats perinatally exposed to methadone had body weights that were comparable to controls.

Motor Activity Behavior:

Methadone-treated animals were generally less active than controls at 21 days in the activity cage and open field tests (Tables 1 and 2). Animals in the gestation, lactation, and gestation-lactation groups made fewer photobeam interruptions than controls and entered fewer squares in the open field. In contrast to the reductions in activity observed at weaning, methadone-exposed offspring were more active than controls at 45 and 60 days of age. Rats treated with methadone only during lactation were significantly more active than controls in both activity cage and open field tests. Furthermore, rats in the gestation group entered more squares in the open field and animals exposed to methadone during both gestation and lactation recorded more photobeam interruptions in the darkened activity cage than controls. In general, males were more active than females at 45 and 60 days, and males became more active with increasing age in comparison to female counterparts.

Table 1. The effect of perinatal methadone exposure on activity cage performance of young rats

Age	Treatment Schedule			
	Control	Gestation	Lactation	Gestation-Lactation
21	132.40	99.12*	107.08*	115.40*
45	97.80	90.68	134.96*	119.18*
60	104.56	128.43	189.50*	138.31*

Values represent mean number of photobeam interruptions in the darkened activity cage in 5 min. N = 16 at 21 days; n = 8 at 45 and 60 days. Significantly different from controls at $p<0.01$ (*).

Table 2. The effect of perinatal methadone exposure on performance in the open field on young rats.

Age	Treatment Schedule			
	Control	Gestation	Lactation	Gestation-Lactation
21	38.23	20.85*	29.31*	18.29*
45	26.78	35.25*	43.79*	24.78
60	23.90	26.78*	34.96*	27.18

Values represent mean number of squares entered in the open field in 5 min. N = 16 at 21 days; n = 8 at 45 and 60 days. Significantly different from controls at $p<0.01$ (*).

Learning Behavior:

Active avoidance. Group differences in the numbers of animals successfully meeting the criterion of 5 consecutive avoidances within 100 test trials were analyzed using the Fisher Exact Probability test (Winer 1971). When data from the three experimental groups were combined and compared with controls, a significantly smaller proportion of methadone-treated rats met criterion (43.5 percent methadone and 87.5 percent controls, $p = 0.037$). Comparisons of control animals with rats from individual methadone treatment schedules revealed that only 33.3 percent of the animals in the gestation and gestation-lactation groups met the criterion of 5 consecutive avoidances in comparison to 87.5 percent of the controls ($p = 0.031$ in both comparisons). Sixty-two percent of the rats in the lactation group met the criterion within 100 trials, and this proportion did not differ significantly from control levels. No significant differences between groups were found for total number of avoidances, footshocks, or crossings from one compartment to another.

Discrimination learning. Group differences in the number of animals successfully meeting the criterion of 9 correct discriminations within 10 consecutive choices were analyzed using the Fisher Exact Probability test. In comparison to controls, a smaller proportion of females exposed to methadone met the criterion (87.5 percent and 36.4 percent, respectively). Only 33 percent of animals in the gestation group and 25 percent of rats in the lactation group met the criterion in comparison to 87.5 percent controls ($p = 0.047$ and $p = 0.01$, respectively). Sixty percent of animals in the gestation-lactation group met the criterion. When the total number of correct discriminations out of 100 were evaluated by analysis of variance, no group differences were detected. Differences between the actual number of correct responses and the expected chance levels were analyzed for each of the four groups using the t-test for single means. On the last 50 discriminations, the percentage of correct responses for each group were as follows: gestation, 53 percent; lactation, 54 percent; gestation-lactation, 64 percent; controls, 62 percent; these percentages differed from chance levels only for animals in the control and gestation-lactation groups (both p's <0.05).

DISCUSSION

The results of a previous investigation on the ontogeny of gross motor development and the maturation of sensory and motor behaviors (Zagon and McLaughlin 1978b) revealed that the ages of initial appearance and 50 percent and maximal appearances of a particular behavior were often delayed several days for methadone-treated offspring in comparison to controls. However, these behavioral responses were eventually achieved by all rats, indicating only transient retardation in preweaning behavioral development. The present results demonstrate that rats treated with methadone in utero and/or during lactation were less active than controls at weaning, but more active by postnatal days 45 and 60. Moreover,

in adulthood, female rats maternally exposed to methadone had an impairment in learning ability. Thus, methadone exposure during gestation and/or lactation has a profound effect on activity levels prior to sexual maturity and cognitive abilities in adulthood, with the magnitude of behavioral alterations related to the schedule of opioid treatment.

The cognitive deficits in adult rats that were perinatally exposed to methadone may be a function of the inability to overcome initial learning deficits, retarded rate of acquisition, and/or failure to maintain attention to appropriate cues. Although the two tests employed in the present study were designed to define learning capabilities, it must be recognized that a number of factors (e.g., emotionality, motivation, physical impairments) may have influenced the results. However, in the present study, drug-treated rats were not found to be blind, undernourished, physically retarded, or unmotivated. It appears that perinatal methadone exposure may not totally disrupt normal behavior but rather exerts a selective influence upon certain aspects of behavioral development and learning abilities, with the degree of functional loss differing among the treatment schedules.

The results of the present investigation may be correlated with clinical observations on children delivered by mothers subjected to methadone. These children tend to have electroencephalographic and behavioral changes consistent with increased central nervous system irritability and lowered overall alertness (Lodge, Marcus, and Ramer 1975; Ramer and Lodge 1975), as well as behavioral patterns characterized by hyperactivity (Ting, Keller, and Finnegan 1975; Wilson 1975) and a high intensity of response (Ting, Keller, and Finnegan 1975). In view of these clinical findings, and our results suggesting that methadone alters both somatic and neurobiological development, it appears that further research is needed to define the long-term consequences of perinatal methadone exposure.

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Narcotic Drug Discriminations by Rhesus Monkeys and Pigeons

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Drug discrimination procedures, which reinforce responding differentially in the presence and absence of drug administration, have demonstrated several important aspects of the behavioral pharmacology of narcotics. Using these techniques it has been shown that morphine-like compounds have discriminable effects that are similar across chemically different classes of narcotics (e.g., Colpaert, 1978). The discriminative effects of morphine-like drugs are easily differentiated from those of a variety of other behaviorally active classes of drugs such as major tranquilizers and sedative hypnotics (e.g., Shannon and Holtzman, 1976). More important, perhaps, is the fact that differences among narcotic analgesics have been shown. Rats and squirrel monkeys trained to discriminate morphine from saline do not generalize completely to cyclazocine, and vice versa (Holtzman *et al.*, 1977). Since marked differences in the interoceptive effects of these drugs in humans have been reported, Holtzman and his colleagues (e.g., Schaefer and Holtzman, 1978) have suggested a strong correspondence between the discriminative effects of these drugs in animals and the subjective effects of the drugs in man.

We were interested in describing the discriminative effects of a variety of narcotics in the rhesus monkey, chosen because of the vast information available on narcotics in this species, and the pigeon, chosen on the basis of convenience for comparative purposes. In terms of drug classification, we were interested in whether we could find distinctive drug classes, based on drug-induced discriminative effects, that would correspond to Martin's hypothesis (Martin *et al.*, 1976) that three receptors mediate the agonist effects of narcotics. In addition, we have investigated the discriminative actions of systemically active narcotic peptides in an attempt to establish a correspondence between structural analogues of enkephalin and Martin's classificatory scheme. Finally, we have studied the discriminative properties of naltrexone in pigeons that were otherwise drug naive. The direct actions of naltrexone responsible for its discriminative effects appear to be different from those of other narcotic agonists and mixed agonist-antagonists.

METHODS

Subjects. White Carneaux pigeons, obtained from Palmetto Pigeon Farm, Sumter, South Carolina, were reduced to approximately 80 percent of *ad libitum* feeding weight and maintained at this weight by reduced feeding supplemental to that earned in the experiments. Rhesus monkeys, obtained from Primate Imports, New York, N.Y., or Mol Enterprises, Portland, Oregon, were reduced to approximately 85 percent of

free feeding weight. They were fed sufficient Purina Monkey Chow after each session to maintain their reduced weights; fresh fruit was provided following most sessions. The monkeys were also given isoniazid (20 mg/day) on sugar cubes. All animals were housed individually and water was freely available in the home cages.

Discrimination training. The discrimination training procedure used in these experiments is similar to that described by others (e.g., Colpaert *et al.*, 1976). The experimental chambers were fitted with two keys and a food receptacle. Programming and recording were accomplished by a Texas Instruments 960A computer and cumulative recorders. The animals were trained to operate the keys by the method of successive approximation, and initially each response was reinforced. Responses on the right or left key were reinforced on successive days depending upon whether drug or saline administration occurred before the session; responses on the inappropriate key had no programmed consequence. The number of responses required for reinforcement was gradually increased across successive sessions until 20 consecutive responses (fixed ratio 20) were required. Responses on the inappropriate key reset the fixed-ratio requirement on the appropriate key. Responding by the monkeys was reinforced by the delivery of a 300 mg banana-flavored Noyes food pellet, while responding by the pigeons was maintained by 4 sec access to a hopper containing mixed grain. Training sessions ended after either 32 (for the pigeons) or 75 (for the monkeys) reinforcer deliveries, or after 1 hour, whichever occurred first.

Animals continued on the training procedure 6 days/week until they met the criteria of emitting less than 40 responses before the first reinforcer delivery and distributing at least 90 percent of the total session responses on the appropriate key for 5 consecutive sessions during which drug and saline injections alternated and then for 4 consecutive sessions during which drug and saline pretreatments were administered in a double alternation sequence.

Dose-effect determinations for training drugs. Following acquisition of the drug/saline discrimination, various doses of the training drug were evaluated for their ability to produce drug-appropriate responding. Throughout these sessions, 20 consecutive responses on either the drug-appropriate or saline-appropriate key were reinforced. In general, testing with different doses of the training drug was conducted on Tues., Thur., and Sat., while further drug/saline discrimination training continued during the remaining daily sessions. If an animal failed to achieve the discrimination criteria, described above, on a given training session, further testing was postponed until these criteria were met on at least two consecutive training sessions.

Cross-drug evaluations. Dose-effect evaluations for a variety of drugs were conducted to establish the ability of these drugs to produce discriminative effects similar to those of the training drugs. Testing was conducted as described above for the training drugs. Single observations per dose were obtained at a variety of doses for each test drug, and in most cases, in each of at least three animals.

Several measures of the discriminative control of behavior exerted by the drugs were obtained. We report here the average dose of each test drug which was required to produce more than 90 percent of the total session responses on the drug-appropriate key.

Drugs. Naltrexone hydrochloride and naloxone hydrochloride were generously supplied by Endo Labs. Ethylketazocine methane sulfonate, pentazocine (base), cyclazocine (base), ketazocine methane sulfonate and meperidine hydrochloride were provided by Dr. W. Michne (Sterling Winthrop). FK 33824 (Tyr-D-Ala-Gly-MePhe-Met(0)-ol) was generously supplied by Dr. D. Roemer (Sandoz). Etorphine hydro-

chloride was provided by Dr. R. Willette (NIDA). Dextrorphan tartrate and UM 1046 (3-cyclopropylmethyl-1,2,3,4,5,6-hexahydro-8-hydroxy -6-methyl-3-benzazocine hydrochloride) were gifts from Hoffmann LaRoche. UM 979 ((-)-5,9-dimethyl-2-(3-furylmethyl)-2'-hydroxy-6,7-benzomorphan), UM 1072 ((+)-(1R/S, 5R/S, 9R/S, 2''R/S)-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan hydrochloride) and quaternary naltrexone were kindly provided by Dr. H. Merz (Boehringer-Ingelheim). Apomorphine hydrochloride was a gift from Merck & Co. Cyclorphan hydrochloride was donated by Dr. M. Gates (University of Rochester). SKF-10,047 was provided by Dr. A. Jacobson (NIH). D-amphetamine sulfate was a gift from Smith, Kline and French. Nalorphine hydrochloride was provided by Lilly. Codeine phosphate and sodium pentobarbital were obtained from University Hospital, Ann Arbor, MI. Morphine sulfate was purchsed from Mallinckrodt (St. Louis); thyrotropin releasing hormone (TRH) from Sigma (St. Louis); and bemegride from Aldrich (Milwaukee).

RESULTS

Assessment of morphine-like and ethylketazocine-like drugs in rhesus monkeys and pigeons. Rhesus monkeys were trained to discriminate either etorphine (0.001 mg/kg, i.m., 40 min before session) or ethylketazocine (EKC; 0.01 mg/kg, i.m., 10 min before session) from saline. Table 1 shows that drugs that produced drug-appropriate responding in monkeys trained to discriminate etorphine from saline, i.e., morphine, meperidine, codeine and the systemically active analogue of methionine enkephalin, FK 33824, did not produce drug-appropriate responding in animals trained to discriminate EKC from saline. Conversely, EKC and SKF-10,047, drugs which produced dose-related EKC-appropriate responding, were inactive as cues in etorphine-trained monkeys. Pentazocine, at behaviorally active doses, did not produce drug-appropriate responding in either group of animals. In the monkey, the following drugs were also fully equivalent to EKC (doses, mg/kg, given in parentheses): cyclazocine (0.02); ketazocine (0.04); cyclorphan (0.05); nalorphine (0.32); and UM 1072 (0.01) and UM 909 (1.0) (two furyl N-substituted benzomorphans that fulfill some of the criteria for kappa-receptor agonist activity, Woods *et al.*, 1978). In addition to the narcotic agonists listed in table 1 which failed to produce EKC-appropriate responding, apomorphine (0.03-0.32 mg/kg), pentobarbital (3.2-17.8 mg/kg), and dextrorphan (1.0-5.6) were not equivalent to EKC.

Table 1

Average dose, mg/kg, of compounds required to produce at least 90 percent of the total session responses on the drug-appropriate key in rhesus monkeys.

Compound (dose range tested, mg/kg)		Training Drugs, Dose (mg/kg)	
		etorphine, 0.001 (n=2)	EKC, 0.01 (n=3)
morphine	(0.1 - 10.0)	1.0	inactive as cue[a]
meperidine	(0.1 - 1.8)	0.7	inactive as cue
codeine	(0.32 - 10.0)	3.2	inactive as cue
FK 33824	(0.1 - 3.2)	2.1	inactive as cue
EKC	(0.003 - 0.03)	inactive as cue	0.01[b]
SKF-10,047	(0.1 - 1.8)	inactive as cue	0.4
pentazocine	(0.32 - 3.2)	inactive as cue	inactive as cue

[a]The majority of responses following the administration of drugs which were "inactive as cues" were made on the saline-appropriate key.
[b]n=5

Pigeons were trained to discriminate either morphine (10 mg/kg , i.m., 10 min before session) or EKC (0.32 mg/kg, i.m., 5 min before session) from saline. The pattern of cross-drug evaluation in the pigeon (table 2) was markedly different from that seen in the monkey. Morphine-trained pigeons showed drug-appropriate responding following injections of EKC and vice versa. EKC was five times more potent than morphine in producing drug-appropriate responding in morphine-trained birds and 24 times more potent than morphine in EKC-trained birds. In addition, drugs that were equivalent only in EKC-trained monkeys (e.g., ketazocine, UM 909, and UM 1072) or in etorphine-trained monkeys (e.g., codeine and FK 33824) produced drug-appropriate responding in both groups of birds. Pentazocine, which had not occasioned drug-appropriate responding in either group of monkeys, produced both morphine- and EKC-appropriate responding in pigeons. While the doses of these drugs needed to produce morphine-appropriate responding were, in most instances, at least twice those required for EKC-appropriate responding, the rank order of potencies of these compounds were virtually identical in the two groups of birds (table 2).

Table 2

Average dose, mg/kg, of compounds required to produce at least 90 percent of the total session responses on the drug-appropriate key in pigeons.[a]

Compound (dose range tested, mg/kg)		Training Drugs, Dose (mg/kg)	
		morphine, 10.0	EKC, 0.32
morphine	(3.2 - 32.0)	7.4	4.8
EKC	(0.03 - 10.0)	1.4	0.2
ketazocine	(0.03 - 10.0)	5.8	1.4
codeine	(3.2 - 32.0)	21.4	17.8
FK 33824	(0.1 - 3.2)	2.5	1.0
UM 909	(3.2 - 32.0)	10.0	12.6
UM 1072	(0.03 - 1.0)	0.5	0.3
pentazocine	(3.2 - 32.0)	19.4	10.0
cyclazocine	(0.32 - 3.2)	inactive as cue[b]	inactive as cue
SKF - 10,047	(1.0 - 17.8)	inactive as cue	inactive as cue
pentobarbital	(5.6 - 17.8)	inactive as cue	inactive as cue
dextrorphan	(3.2 - 32.0)	inactive as cue	inactive as cue

[a]Each compound was studied in at least three subjects.

[b]The majority of responses following the administration of drugs which were "inactive as cues" were made on the saline-appropriate key.

Behaviorally active doses of cyclazocine, SKF-10,047, pentobarbital, and dextrorphan were not equivalent to either morphine or EKC in the pigeon. The inability of cyclazocine and SKF-10,047 to produce EKC-appropriate responding in the pigeon is in direct contrast to the effects of these drugs in EKC-trained rhesus monkeys.

Assessment of the discriminative effects of naltrexone in pigeons. Pigeons were trained to discriminate naltrexone (32 or 56 mg/kg i.m., 10 min before session) from saline. Each of ten pigeons acquired the discrimination. The results of cross-testing with a variety of agents in an attempt to characterize the naltrexone cue are shown in table 3. Naloxone produced more than 90 percent drug-appropriate responding (i.e., complete generalization) in 4 of 5 birds. In these birds naloxone was equipotent to naltrexone. On the other hand, EKC produced less than 10 percent naltrexone-appropriate responding in each of the pigeons tested. Cyclazocine, amphetamine, bemegride,

Table 3

Drugs evaluated in pigeons trained to discriminate naltrexone (32 or 56 mg/kg) from saline.

Drug (dose range tested, mg/kg)	Number of Birds Tested	Numbers of Birds Showing Various Degrees of Naltrexone-Appropriate Responding		
		Complete ⩾ 90%*	Intermediate 11-89%*	Absent ⩽ 10%*
naltrexone (3.2 - 56.0)	10	10 *(28)***	—	—
naloxone (10.0 - 56.0)	5	4 *(25)*	1	—
UM 979 (3.2 - 32.0)	5	2 *(7)*	2	1
UM 1046 (3.2 - 17.8)	5	2 *(8)*	2	1
cyclazocine (0.32 - 5.6)	5	—	3	2
EKC (0.32 - 10.0)	3	—	—	3
quarternary naltrexone (10.0-56.0)	5	1 *(32)*	1	3
TRH (3.2 - 32.0)	3	1 *(10)*	1	1
bemegride (1.0 - 10.0)	3	—	1	2
amphetamine (0.32 - 3.2)	4	—	1	3

*Values refer to the percentage of the total responses during the session which were distributed on the naltrexone-appropriate key.

**Given in parentheses is the average dose, mg/kg, required to produce at least 90% naltrexone-appropriate responding.

quaternary naltrexone, and TRH caused little or only intermediate amounts of naltrexone-appropriate responding in most of the birds, although quaternary naltrexone (32 mg/kg) and TRH (10 mg/kg) each produced complete generalization in one pigeon. UM 1046, a compound that produces a syndrome resembling narcotic abstinence in narcotic-naive monkeys (Valentino *et al.*, 1978), and UM 979, a drug with narcotic-antagonist properties, both produced more than 90 percent naltrexone-appropriate responding in 2 of 5 pigeons, and intermediate levels of drug-appropriate responding in two others.

DISCUSSION

The data reported here support the general proposition that drug discrimination techniques may be used to distinguish among different types of narcotics. Our results with EKC and etorphine in the rhesus monkey are similar to those of Holtzman and his colleagues (Holtzman *et al.*, 1977; Schaefer and Holtzman, 1978) who studied the discriminative effects of morphine and cyclazocine in the squirrel monkey. There is general agreement between our data and theirs where there are direct comparisons; they found that cyclazocine-trained squirrel monkeys showed drug-appropriate responding to ketazocine but not to morphine. We have used EKC as a training drug rather than cyclazocine because EKC does not appear to be an antagonist of morphine, and yet, the discriminative effects of cyclazocine, ketazocine, and EKC are similar in these two species of primates. Of considerable importance to us was the fact that two n-furyl substituted benzomorphans, UM 909 and UM 1072, which were predicted to be compounds with EKC-like activity (Woods *et al.*, 1978), produced EKC-appropriate responding in the rhesus monkey. It is quite possible that we can use the distinctiveness of the EKC cue to specify the structure-activity characteristics of drugs with EKC-like agonist activity. Drugs classified in this way can then be used to examine the substrates of behavioral actions associated with EKC-like compounds. The fact that the pigeon appears to lack the ability to discriminate morphine-like from EKC-like compounds under these conditions (table 2; Herling *et al.*, 1979) may reflect the absence

of a necessary substrate. It is obvious that further drug and substrate differences between the pigeon and the rhesus monkey may be helpful in determining mechanisms of action for these drug classes.

The pigeon is able to distinguish the administration of naltrexone from saline, although doses required to establish this drug discrimination are quite high (e.g., 32 mg/kg). At these doses, the antagonism of morphine by narcotic antagonists may be limited by the antagonist's direct action on behavior (e.g., Downs and Woods, 1976). Thus while it may be appealing to invoke interference with an endorphin system as the basis of the discriminability of naltrexone, only further pharmacological analysis will delineate drugs that share common discriminative properties with naltrexone and drugs that might block its discriminative effects. Nevertheless, the discriminative effects of the naltrexone cue appear clearly distinct from other narcotic cues that have been established in the pigeon.

Our findings with FK 33824 are of considerable interest; the initial subjective reports of its effects in man indicated that it appeared somewhat unlike morphine (von Graffenried *et al.*, 1978). Nevertheless, the behavioral pharmacology of the peptide in animals suggests strong morphine-like effects (e.g., Roemer *et al.*, 1977; Hill *et al.*, 1978), and the discriminative effects of the drug in the rhesus monkey and pigeon suggest common discriminative elements with morphine (tables 1,2). We have, on the other hand, found that FK 33824 was self-injected by rhesus monkeys at rates considerably below codeine and morphine and only slightly above saline (Woods *et al.*, 1979). An examination of factors which dissociate the discriminative and reinforcing effects of narcotic-like neuropeptides is an interesting subject for further research.

In terms of our overall objectives we have found strong evidence in the rhesus monkey for distinctive discriminative cues for *mu* (morphine-like) and *kappa* (EKC-like) compounds, in accord with Martin's classification. The sigma agonist, SKF-10,047, was EKC-like in the monkey. In the pigeon, morphine and EKC appear to share common discriminative effects; and neither cyclazocine nor SKF-10,047 is a member of this class, although both drugs are EKC-like in the rhesus monkey. It is possible that in the pigeon the bases for the discriminative effects of cyclazocine and SKF-10,047 are related to the mechanism of action responsible for the sigma-like effects of these drugs described in the dog by Martin and his colleagues.

Our findings with naltrexone in the pigeon establish this drug as a cue for the first time in a naive subject. A full characterization of the discriminative effects of pure antagonists will have important theoretical implications for the classification of narcotic drugs in both the naive and dependent state. The initial findings with FK 33824 suggest that the combined use of a discriminative and reinforcing stimulus analysis of enkephalin analogues (Woods *et al.*, 1979) may be helpful in establishing the similarity of neuropeptide actions to those of other narcotic drugs.

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Effects of Closing the Bakersfield Methadone Clinic

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In California, methadone maintenance programs have come under pressure in the wake of Proposition 13, and two programs, with a total of 920 clients, have recently closed. Earlier, in September 1976, the only methadone clinic in Bakersfield was closed. Since the nearest continuing clinic was in Tulare at a distance of 70 miles, this provided an opportunity to measure the individual and social impact of involuntary termination of methadone maintenance.

The communities and clients served were quite similar. The male samples were approximately 50% white and 50% Chicano (white of Mexican descent); the female samples were approximately 80% white. An average of 6 years elapsed between postaddiction (N) and initial methadone maintenance entry (M) for the males, and 5 years for the female samples. The mean time from M to methadone discharge (D) (July, August or September 1976) was 28 months for the Bakersfield males and 12 months for the female sample. For comparison, a dummy discharge date of August 31, 1976 was chosen for the Tulare sample. The mean number of months from M to D for the Tulare male and female samples were 30 and 36 respectively. Thus, the only significant predischarge difference between the Bakersfield and Tulare samples was the length of time on methadone for the female groups.

Followup interviews[1] were conducted between August 1978 and March 1979--an average of 26 months after the methadone discharge or dummy discharge date. Of the combined samples, 95% were located and interviewed. Two of the Bakersfield sample were deceased--both from drug overdoses--and one of the Tulare sample died from nondrug causes. There were three refusals and four not located.

Of the 94 Bakersfield respondents interviewed, only 11 had reentered a methadone program by the time of interview (I)--some two years after the clinic closure. Eight individuals transferred directly and three entered at a later date. Seven were enrolled at I.

Of the 83 Tulare respondents interviewed, 42 (51%) were on methadone maintenance continuously from September 1976 to I, and another 2 were enrolled at I after a period off the program. During the period, D-I,

the Tulare sample spent 73% of its nonincarcerated time on methadone compared to 8% for the Bakersfield group.

The first half of Table 1 compares the status and behavior of the Bakersfield and Tulare samples for the period D to I. The data are shown in terms of the percent of the sample involved in the status or behavior at sometime during D to I; and, for daily narcotic use and employment, the mean percent of the nonincarcerated time so involved. The latter is the mean of the individual percentages, including those with zero time involved.

Overall, the percentages of Bakersfield respondents arrested, incarcerated and on parole or probation is about twice that for the Tulare sample. Probably the most relevant variable is the number of Bakersfield clients who became readdicted to heroin, and the percent of time spent in this state. Slightly over one-half of both the male and female samples reported addiction at sometime after termination. If the eight who transferred directly to other methadone programs are excluded, 60% of the male and 56% of the female samples became readdicted subsequent to discharge. Of the combined Tulare sample of 83, 26 (31%) reported some daily illicit narcotic use during D to I. Of these, 22 were discharged from the methadone program prior to I; and, for 13 all daily use was subsequent to discharge. Of the 41 discharged from the Tulare program, 3 were incarcerated the entire period to I, and 39% of the remainder used narcotics daily at sometime subsequent to discharge.

The second half of Table 1 presents the status at the time of interview. Self-reported use of narcotics and other illicit drugs in the four weeks preceding I was only marginally higher for the Bakersfield sample; self-reported daily use was quite low for both groups. Urine specimens were obtained from all but seven of the 154 respondents not incarcerated. Analysis was only for morphine (heroin), using immunoassay techniques substantially more sensitive than those of the routine commercial laboratory tests (cutoff was 30 ng. morphine per ml.) (Catlin 1973). There was 91% agreement between the urine results and self-reported opiate use within the seven days prior to I. The Bakersfield rate of positive urines plus refusals was about twice that for the Tulare samples, indicating more frequent use for the former. Of the 14 Tulare respondents testing positive--or refusing a specimen--only two were from individuals currently on methadone maintenance.

There is some indication of greater stability among the Tulare samples as evidenced by the higher percentages supporting dependents and living in the same residence for the past 12 months.

The Bakersfield respondents reported their own assessments of the effect of the clinic closing on various areas of their lives. Seventy-two percent stated that they increased heroin use--at least as an aid to detoxification from methadone. Twenty percent said they substituted other drugs, mainly tranquilizers and barbiturates, and 15% increased alcohol consumption. Twenty-six percent reported employment dislocation, 30% health problems (prolonged withdrawal), 18% marital or social difficulties, and 28% increased criminal activity. Fifty-six percent felt the program closure was the indirect cause of one or more arrests. As an overall assessment of their methadone experience, 81% of the

Table 1

Status or Behavior Subsequent to Methadone Discharge

Status or Behavior	Males		Females	
	Bak. N=55	Tulare N=56	Bak. N=39	Tulare N=27
Discharge to interview (D-I)				
% arrested[a]	73*	43	74*	33
% incarcerated >30 days	65*	32	54*	22
% on legal supervision	60*	34	67*	15
% using narcotics daily	55*	32	54	30
Mean % time using daily	30*	13	20	9
% abusing alcohol[b]	64*	43	44	22
% dealing drugs	62*	32	41	30
% reporting property crime	22	16	26	41
Mean % time employed	51*	68	32	26
% receiving welfare	15	23	44	48
Status at time of interview (%)				
Incarcerated	15	14	10	11
On methadone maintenance	4*	56	14*	71
Drug use last 4 weeks (exc. mari.)				
Any use	49	50	37	33
Any narcotic use	40	35	31	25
Daily narcotic use	9	6	9	8
Urinalysis results				
Positive (morphine)	30	15	31	21
Refused specimen	4	4	9	0
Reported use; refused or positive urine	51	42	51	33
>40 oz. 85 proof alcohol in last 7 days	26	19	9	0
Supporting dependents	43	60	41	54
Living in current residence >12 months	21*	44	20*	46

Note: Mean % times using daily and employed are based on nonincarcerated time from discharge to interview; and all status-at-interview percentages except that for incarceration are based on the nonincarcerated samples.

*Difference between Bakersfield and Tulare samples significant ($P<.05$).

[a]Arrest data are for period methadone discharge to April 1978.

[b]Alcohol abuse is defined as drinking at least seven drinks or equivalent over a six-hour period two or more times per week.

Bakersfield sample stated they were glad they enrolled in the program compared to 88% for the Tulare group.

Social costs during D to I were calculated for those variables which could be readily measured in economic terms. The entries in Table 2 are the aggregate costs for treatment, incarceration, etc. divided by the number of respondents in the sample. Treatment costs are $200 per month for methadone maintenance and $600 for therapeutic communities--detoxification and other treatment costs are not included. Arrest and court processing is estimated at $900 per arrest. Jail, civil commitment center and prison costs are $480, $600 and $910 per month respectively. Probation, civil addict parole and prison parole costs are $50, $175 and $130 per month. The cost of forgeries and robberies is the amount of money realized by the respondent. The reported income from burglaries and thefts is multiplied by three to adjust for the discounting associated with the disposal of stolen goods. Welfare income is that reported by the respondent.

Table 2

Social Costs ($00) Per Respondent from Methadone Discharge to Interview

Costs	Males		Females	
	Bak. N=55	Tulare N=56	Bak. N=39	Tulare N=27
Treatment	6	31	6	39
Arrests and court processing[a]	16	10	19	6
Incarceration	34	30	19	7
Legal supervision	8	5	9	1
Property crime[b]	62	33	12	38
Welfare	8	7	16	41
Total	134	116	81	132
Mean annual costs	62	53	37	63

Note: The data in this table are the aggregate costs divided by the number of respondents--not the means of individual costs.

[a]Arrest data were collected from methadone discharge to April 1978, but are prorated to the time of interview.

[b]Excludes crime data for one Tulare male and one Tulare female.

The higher treatment costs for the male Tulare sample are offset by the greater criminal justice and crime costs for the Bakersfield group. The Tulare female sample exhibits higher treatment, crime and welfare costs than that for the Bakersfield group, and the total annual costs per respondent are some $2600 higher. The female income was augmented by prostitution. Twenty-three percent of the Bakersfield and 26% of the Tulare female samples reported prostitution during the period, D-I, and the average annual income across all female respondents was $2200 and $1300 respectively.

It should be noted that the crime costs are based on the reports of a

small number of persons (for the female samples, 9 Bakersfield and 11 Tulare respondents reported property crimes). In a previous study employing a much larger sample, both property crime arrest and self-reported crime were strongly related to the proportion of time addicted to heroin (McGlothlin, Anglin, and Wilson 1978).

The data presented in Tables 1 and 2 have focused on the interval D to I. Similar data were collected for the average interval of 5-6 years from first daily narcotic use (N) to initial entry into a methadone program (M); and from M to D--an average interval of 2.5 years for the male samples and 1-3 years for the female groups. The mean percent of nonincarcerated time using narcotics daily during N-M was 80 for the combined male and female Bakersfield sample, and 76% for the Tulare sample. The corresponding percentage for M-D was 13 for both samples. Annual social costs were calculated in the same manner as in Table 2 for periods N-M and M-D. For Bakersfield, the values were $12,200 and $6100 respectively; and for the Tulare sample, $17,600 and $8200. Thus, while the results presented in Table 2 do not show a social cost advantage for continuing methadone for clients already in treatment for an average of 2-3 years, the pre- to during-methadone cost data do show a large improvement.

In summary, the results presented in Table 1 clearly show that the Bakersfield clients performed worse than the Tulare sample subsequent to the clinic closure. Even in the absence of a corresponding social cost advantage for the Tulare sample during the D to I period, the maintenance approach would appear preferable to one requiring such extensive criminal justice intervention--not to mention the possible prevention of the two drug overdose deaths that occurred in the Bakersfield sample. Had the extent of postdischarge heroin addiction and associated criminal behavior in the Bakersfield sample returned to a point approaching the premethadone level, the social cost would have exceeded that for the Tulare group by a substantial margin. Why did this not occur? The most favorable interpretation is that the beneficial effects of treatment continued to limit the rate of addiction after the involuntary termination of methadone. On the other hand, the apparent large declines in addiction rates found in followups of untreated samples would suggest that other factors are also involved (NIDA 1977; Simpson, Savage and Sells 1978).

One explanation is the existence of an especially active Bakersfield Heroin Impact Project (HIP) at the time of the clinic closure. The Bakersfield HIP force was initiated in May 1976--five months before the clinic closure--and during the next 12 months, made 852 arrests compared to a total of 166 misdemeanor drug arrests in 1975 (Bureau of Criminal Statistics 1978). The arrest records for the Bakersfield clients show that 18 were arrested on under-the-influence charges for the 6-month period during and immediately following the clinic closure (July-December 1976). Thus, the threat of arrest, incarceration and subsequent probation supervision may well have limited the amount of time addicted.

A second factor which may have limited the return to heroin addiction after discharge is the current very low purity and high price of street heroin. Heroin overdose deaths and other indices of use have shown a sharp decline since mid-1976 (Drug Enforcement Administration and NIDA

1978), and the poor quality of heroin is thought to be a major reason. Responses obtained in the present study support this hypothesis. Of the 57 Bakersfield respondents indicating recent experience in acquiring heroin, 52% said that as a result of the very poor quality they were less interested in using, or that it wasn't worth it. Parenthetically, 19% of the 86 Bakersfield and Tulare respondents enrolled in treatment in the two years prior to interview indicated that these considerations were partly responsible for their continuing treatment.

In summary, it seems reasonable to conclude that the impact of the Bakersfield clinic closing, as reflected by the readdiction rate and associated behavior, is a minimum estimate. The additional police pressure, and the poor quality and high cost of heroin, probably minimized the extent of readdiction to heroin.

Whatever the causes of the relatively low postdischarge rate of heroin addiction among the Bakersfield sample, it raises the question of the extent to which methadone programs may be unnecessarily prolonging the addiction to a narcotic--albeit one licitly obtained. In spite of a general bitterness about the closure of the clinic, 27% of the respondents stated that, in retrospect, they felt they had benefited since it enabled them to discontinue methadone maintenance as well as heroin. Only 26% indicated they would enroll in methadone maintenance if it were available; although a larger number would undoubtedly do so if they became readdicted to heroin. At the time of the interview, 73% of the Bakersfield sample were not incarcerated, and did not admit addiction to either a licit or illicit narcotic. The comparable percentage for the Tulare group was 28.

On the other hand, 54% of the Bakersfield sample became readdicted to heroin; 73% were arrested; 61% were incarcerated for more than 30 days; and 2 died of drug overdoses. Certainly, there were a number of instances where an individual who was leading a stable life on methadone was thrust back into the chaotic life of the street addict. In considering whether or not to force a stable methadone client to detoxify, the clinic director must weigh these risks against the treatment costs and the possible benefits which may result to the individual from terminating methadone dependence. Interestingly, comparing those who did and did not become readdicted during D to I showed virtually no difference with respect to sex, age, time on methadone or methadone dose level prior to detoxification (mean=38 mg.). Those becoming readdicted were more likely to be Chicano and to have an earlier and more extensive pretreatment criminal justice involvement. Those reporting little or no illicit narcotic use while on methadone were significantly more likely to avoid addiction after discharge.

Given the dilemma of whether to maintain a stable client indefinitely, or risk serious detrimental effects from involuntary termination, an approach of encouraging detoxification with an accompanying flexible readmission policy may be the best solution.

FOOTNOTE

1. The interview was adapted in part from a schedule developed by Nurco and colleagues (Nurco et al. 1975).

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An Improved Evaluation Instrument for Substance Abuse Patients: The *Addiction Severity Index*

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INTRODUCTION

The mental health field has traditionally profited from attempts to divide patients into homogeneous groups based upon relevant symptomatology. As in the examples of psychosis and especially affective disorders, such diagnostic classifications have added focus to research efforts, and improved the specificity and effectiveness of treatments. However, within the field of substance abuse treatment, efforts to evaluate and classify the patient population have been far less useful. In our view, these less than satisfactory attempts are due in part to a somewhat restricted view of addiction, and in part to failure in developing a standardized, reliable and valid evaluation instrument which would be suitable for use with both alcoholic and drug addicted patients. The design for such an instrument was first proposed in an NIDA conference on Treatment Efficacy (O'Brien 1975; Fonaroff et al. 1978) and has led to the development of a multi-dimensional clinical research instrument for addicted clients, the Addiction Severity Index (ASI) (McLellan et al. 1979a,b). The present paper reports the results of reliability, validity and patient classification studies using the ASI.

DESCRIPTION OF THE ADDICTION SEVERITY INDEX

Design: The design of the ASI is based upon the premise that addiction must be considered in the context of those treatment problems which may have contributed to and/or resulted from the chemical abuse. The objective of the ASI is to produce a problem severity profile of each patient through an analysis of six general areas which commonly result in treatment problems. These include: (1) Chemical Abuse, (2) Medical, (3) Psychological, (4) Legal, (5) Family/Social, and (6) Employment/Support. The severity of each of the treatment problem areas is assessed individually and independently through two types of information.

Objective Information: The data collected within the objective section detail the number, intensity, and duration of problem symptoms in each of the six areas. Verifiable data from objective questions

as well as test results, laboratory reports, physical examinations, and psychological interviews are collected to develop a factual representation of the patient's life pattern in each of the six areas.

Patient's Judgments of Severity: The second section of each problem area is designed to measure the subjective intensity of problem symptoms. The patient is requested to rate, using a five-point scale, the extent to which he has been bothered by problems in each of the six areas, and the extent to which he feels that treatment for those problems is important. The time frame for these evaluations is the previous 30 days.

SEVERITY RATINGS

The data from the objective information and patient-report section of each problem area are integrated by the interviewer to produce the severity ratings. These six severity ratings form the basis for the clinical profile of each patient, providing a diagnostic/evaluative summary of the patient's treatment needs. In this respect the ASI has utilized the approach taken by the Health-Sickness Rating Scale (Luborsky 1962; Luborsky 1975; Luborsky and Bachrach 1974). Both instruments rely on objective information and analyses of problem components as a means toward developing clinical ratings of severity. While the HSRS uses a 100-point scale anchored by descriptions, the ASI uses a ten-point (0-9) unanchored scale.

ADMINISTRATION

The ASI may be administered to all types of substance abuse clients by an easily trained technician in an average time of 25-30 minutes. The interview was designed for initial use shortly after admission to treatment, and then for repeated administrations at subsequent followup periods. The ASI is administered most effectively under conditions of privacy and confidentiality where the interviewer maintains an atmosphere of professional concern and warmth. A brief introduction to the interview explaining the design of the ASI, and the use of the patient rating scale, is considered necessary to the development of a productive and valid interview.

The results of 750 admission interviews from 421 alcoholics and 329 drug addicts, indicate that the ASI is applicable to, and often appreciated by, the majority of patients. Many have reflected positively upon the patient-estimate sections, commenting that they have been able to focus upon the individual aspects of their addiction. Only 11 of these 750 interviews were discarded for invalid information, and only 14 others were eliminated due to inadequate comprehension.

VALIDITY

We have performed preliminary assessments of validity for each of the problem severity scales by correlating the scale scores with other independent items having clear relationships to the particular

problem area. These correlation coefficients are presented in table I. As can be seen, each of the severity scales correlates with the comparison items at mid range or higher levels, and in the expected direction, with the comparison items. Although these early results are encouraging it should be clear that these data are only indicative of presumptive or face validity.

RELIABILITY TESTING

The reliability of the Addiction Severity Index was initially assessed during the performance of our evaluation study (McLellan et al. 1977) and was reassessed periodically during that study and in two others (Woody et al. 1977; McLellan et al. 1979). In the basic design one research technician has conducted an interview while three others rated the videotaped presentation. The results to be reported are based upon the judgments of these four bacculaureate level research and rehabilitation technicians with little previous interviewing experience. The data for 25 male veteran patients rated by these judges are presented in table II.

The first line of table II shows the mean per-judge reliability coefficients (Spearman-Brown formula; see Winer 1962) calculated for the first 16 patients interviewed. As can be seen, the coefficients are particularly high given that the judges had had very little experience with substance abuse patients or the ASI. While it seems likely that the forced uniformity of the procedure (one interview instead of four) may have artificially enhanced the reliability, we were mainly concerned that the high coefficients were the result of a systematic bias developed over the course of training in the inexperienced judges. To test for this possibility, we repeated the reliability assessment procedure following a two-month, and then a four-month period of independent on-the-job interviewing experience by the four judges. The results for these additional reliability tests are presented in the second and third lines of table I, and as can be seen, no significant decrements were observed in the average reliabilities for each scale.

Given the generally high level of reliability demonstrated, we attempted to determine if there were significant differences in reliability between several obvious subgroups of our substance abuse clients. The second section of table II presents reliability coefficients for these 25 patients divided into alcoholic (n=14) and drug addict (n=11) subgroups. Again the reliability results for each group are quite high. These 25 subjects were then divided on the basis of age, and by their total (sum of six scales) severity scores, to determine the extent of difference in reliability of severity estimates. The results of these comparisons are presented in the third and fourth (respectively) sections of table II, and again the coefficients remain high, with no significant differences between the groups on any of the scales.

One important issue raised by the uniformly high reliability across the six problem scales is the extent to which the problem areas are interrelated. If the problem areas and their severity estimates are

highly related to each other then the determination of one severity estimate (i.e., substance abuse severity) might exert a controlling influence upon the other scales, thereby accounting for their high reliabilities. In order to determine the nature and extent of the relationships between the scales, correlation coefficients were calculated on the ASI's of 524 male veteran substance abuse clients. As can be seen in table III, the intercorrelations are generally quite low with the exception of the psychological and family/social scales (.41), indicating a considerable degree of independence between the scales. This result was much different from our experience with the Health-Sickness Rating scale where the components of mental health tended to be highly intercorrelated and highly correlated individually with the global rating (Luborsky 1962). As a further test of these relationships we performed the same analysis with several obvious subgroups of the population. These included alcoholics, drug addicts, those over 45 years old, those less than 45 years old, blacks and whites. While several small differences in the interrelationships of these ratings were noticed between the subgroups, the majority of the coefficients remained quite low.

The independence of the six problem areas indicates that the treatment problems presented by addicted patients are not necessarily related to the severity of their chemical abuse. This result suggests that the proposed method of analyzing a patient's total condition by the severity of his component problems is both reasonable and necessary for the development of an effective treatment plan.

UTILITY OF THE ASI

The findings from our analysis of ASI scale intercorrelations suggested that our substance abuse population may be composed of several subgroups of patients, each with a somewhat different pattern of treatment problems. As a test of this possibility, and as a means of assessing the utility of the ASI in differentiating patients into relatively homogeneous subgroups, we performed a cluster analysis on 150 randomly selected patients (75 alcohol, 75 drug), using their six ASI scale values as independent variables. In the particular type of cluster analysis selected (Hartigan 1975; Brown and Dixon 1977) groups (clusters) of patients are formed by minimizing the differences (Euclidean distance) between values on each of the scales within the clusters and maximizing the differences in mean values of the scales between clusters. Since we had no theoretical or mathematical rationale for variable weighting of the scale values, all six scales were treated equally in the analysis.

The results of this analysis are presented in table IV, which shows the resulting six, statistically different ($p < .01$), clusters and the mean values for their six problem severity scales. The differences between clusters in the scale severity scores explain, in large part, the low intercorrelations between the scales when the data are ungrouped (table IV). Analyses of scale intercorrelations within each of these clusters indicate rather high (.75-.90) relationships between three or four scales within each cluster.

The mean severity profiles of the clusters are interesting since

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they correspond with several "types" of patients which are commonly seen during treatment. For example, cluster #4 corresponds to the "medical model" of addiction as a progressive syndrome. The average profile for this group is demonstrative of patients with significant problem severity in all aspects of their condition. In contrast, cluster #3 depicts patients with a high substance abuse severity, but few additional problems. Cluster #5 is especially noteworthy since the mean profile of this group indicates that while substance abuse may be their presenting complaint, it is not their most severe treatment problem.

In summary, the results of this cluster analysis do suggest the utility and effectiveness of the Addiction Severity Index as an evaluative method for differentiating clients into subgroups with different patterns of treatment problems. It should be clear that the particular clusters presented here may not be indicative of groups found in other clinics, especially programs with adolescents, women, nonveterans, etc. However, they suggest that the ASI scales can be effective in differentiating a substance abuse population into whatever appropriate subgroups exist.

CONCLUSIONS

We have attempted to show the need for a standardized clinical research instrument, suitable for general use in the study and treatment of substance abuse. This instrument should have the capacity to analyze the total addiction profile into its component treatment problems, and to reliably and validly estimate the severity of each of these problems. Our early results with the Addiction Severity Index suggest that it may have the potential for being such an instrument.

Clearly, much work is still required to further establish the reliability and validity of the instrument with other patient populations, and other teams of judges. Despite the considerable work remaining, we expect that the ASI should fill the need for an instrument to assist the clinician in integrating and summarizing the background and current status of patients. In addition we feel the ASI may be of special assistance in determining a treatment plan for the individual client.

We are also encouraged by the potential benefit of the ASI to research in the field of addiction. After proper standardization we expect the ASI to be suibable for general use in clinical research and thus facilitate greater comparability of results (Rittenhouse 1978). In addition the ASI may permit more effective matching of patients at the start of experimental treatments, and a more comprehensive evaluation of posttreatment outcome.

REFERENCES

Due to space constraints references are available from the senior author.

TABLE I

VALIDITY OF ASI SCALES

524 MALE VETERAN SUBSTANCE ABUSE CLIENTS

SCALE	INDEPENDENT VARIABLES	CORR. COEFF.
ABUSE	TIMES O.D., BLACKOUT, SEIZURE	.72
	TOTAL YRS. REGULAR USE ALC/DRUGS	.66
	AMOUNT SPENT ON ALC/DRUGS PER WEEK	.54
MEDICAL	NUMBER OF CURRENT MEDICAL SYMPTOMS, VA REVIEW SYSTEM	.69
	AMOUNT OF MEDICAL DISABILITY/PENSION	.60
	NUMBER OF PREVIOUS HOSPITALIZATIONS	.58
EMP-SUP	RATIO OF EARNED TO UNEARNED INCOME, PAST MONTH	-.64
	MONTHS OF CONTINUOUS FULL TIME WORK	-.62
	HOLLINGSHEAD S.E.S. RATING	.56
FAM-SOC	PROPORTION OF FRIENDS W/ABUSE PROBLEMS	.52
	PROPORTION OF FAMILY W/ABUSE PROBLEMS	.48
	NUMBER OF CLOSE FRIENDS	.43
LEGAL	TOTAL CONVICTIONS	.71
	TOTAL MONTHS INCARCERATED	.68
	PROPORTION OF INCOME GAINED LEGALLY	.62
PSYCHOLOGICAL	MAUDSLEY N SCALE	.64
	BECK DEPRESSION INVENTORY	.61
	HAMILTON DEPRESSION SCALE (N=111)	.58

TABLE II

INTER-RATER RELIABILITY COEFFICIENTS
ON PROBLEM SEVERITY RATINGS*

TEST	SUB. ABUSE	EMP./ SUP.	MED.	LEGAL	FAM./ SOC.	PSYCH.	AVE.
(Sept.) Subjects 1-16	.90	.89	.92	.88	.85	.92	.898
(Nov.) Subjects 17-19	.89	.90	.92	.89	.86	.91	.905
(Jan.) Subjects 20-25	.91	.91	.90	.90	.86	.92	.906
All Subjects 1-25	.90	.90	.92	.89	.86	.92	.918
Alcoholics N=14	.90	.91	.93	.88	.85	.92	.908
Drug Patients N=11	.91	.88	.91	.90	.87	.91	.905
Age < 35 N=11	.90	.89	.91	.90	.84	.89	.885
Age > 35 N=14	.91	.91	.91	.88	.87	.93	.912
Cumulative Sev. Score > 30 N=15	.90	.91	.93	.89	.86	.94	.915
Cumulative Sev. Score < 30 N=10	.89	.88	.91	.89	.85	.90	.886

* Ratings were based upon 4 judges; per-judge reliability coefficients were calculated by the formula:

$$\frac{MS_B - MS_W}{MS_S + (K-1)\,MS_W} = R \qquad \text{(Winer, 1962)}$$

TABLE III

ASI SEVERITY RATINGS

CORRELATION COEFFICIENTS

524 MALE, VETERAN, SUBSTANCE ABUSE PATIENTS

	MEDICAL	EMP/SUP	LEGAL	FAM/SOC	PSYCH
ABUSE	.10	.19	.09	.14	.18
MEDICAL		.26	.06	.16	.34
EMP/SUP			.27	.21	.17
LEGAL				.15	.11
FAM/SOC					.41

TABLE IV

ASI SEVERITY RATINGS
ANALYSIS OF PATIENT SUB-TYPES
IN
150 MALE, VETERAN, SUBSTANCE ABUSE PATIENTS
(75 ALCOHOLIC - 75 DRUG ADDICTED)

CLUSTER	N	ABUSE	MEDICAL	EMP/SUP	LEGAL	FAM/SOC	PSYCH
1	40	6.5	1.5	5.5	3.5	5	2
2	32	7	2	4.5	1	5	5.5
3	27	6	2	2	1.5	1.5	2
4	25	7	5	6.5	5	6	7
5	14	5	1	2.5	4	5.5	6.5
6	12	5	4.5	2	5	5	5

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Development of Psychiatric Disorders in Drug Abusers: Relation Between Primary Drug and Type of Disorder

McLellan, A. T.; Woody, G. E.; O'Brien, C. P.

INTRODUCTION

In the course of evaluating the long term effectiveness of our drug abuse treatment program, we discovered a sample of substance abuse patients who had been initially admitted to inpatient drug-free treatment at this facility during 1971-1972, and had demonstrated a pattern of virtually continuous drug abuse since that time, punctuated only by their multiple readmissions for further treatment. The readmission records of these patients provided information on intake status, psychiatric assessments, psychological testing and within-treatment progress over the course of the past six years, offering an opportunity to examine the longitudinal relationships between patterns of prolonged substance abuse and the development of psychiatric disorders.

METHOD

Subjects - Subjects were 51 male veterans who had been admitted to inpatient drug abuse treatment at the Coatesville VA Medical Center during 1971-1972, and who had been readmitted for treatment at that facility a minimum of six times since 1972. These subjects were of course selected retrospectively during 1978, and while this sample of chronic readmissions represents only 9% of the total patients admitted to treatment at that facility during the period July 1971 through June 1972 it represents all of the patients who met the readmission frequency criterion.

These subjects were divided into three groups based upon their primary drug preferences in 1971-1972. Subjects in group I (n=11) had reported primary use of psychostimulants including hallucinogens, amphetamines and inhalants. Subjects in group II (n=14) had reported primary use of psychodepressants including barbiturates, benzodiazepines, and sedative hypnotics. Group III subjects (n=23) had reported primary use of narcotics, such as heroin, methadone, and synthetic opiates.

Procedure - The purpose of the present research was to examine the

course of change in drug problems and psychological status within these three groups over the course of their six year treatment history.

1978 COMPARISONS

An examination of the 1978 admission data for these subjects indicated significant generalized deterioration within groups, as well as significant specific changes in psychological status between groups (table I).

Group I - Psychostimulants - Although the subjects in this group could still be characterized as psychostimulant users generally, there was evidence of significant and pervasive change in their patterns of abuse by 1978. For example, the majority (79%) of these subjects reported regular use of amphetamine or methylphenidate injected intravenously (see table II), and little regular use of psychedelics or hallucinogens (with the exception of marijuana). In addition, 28% reported irregular use of psychophysiologically dissimilar chemicals (i.e., barbiturates, benzodiazepines) in addition to amphetamine. This pattern of change in drug preference away from psychedelics to amphetamine has been reported by Smith and his colleagues (Smith and Fisher 1969; Shick et al. 1972) and appears to represent a legitimate change in preference rather than a change in availability. These subjects reported very little (2.3%) narcotic use, and no period of physical addiction.

As can be seen in the comparison of 1972-1978 psychological testing for these subjects (table I), the group results showed significant increases in psychological symptoms ($F=12.12$, df 1, 274, p .001) between the years. Although no decrements in intellectual or conceptual function were evident, the MMPI data demonstrated pervasive differences, especially in the areas of general pathology (F), hysteria (Hy), Paranoid (Pa), Schizophrenia (Sc), and Mania (Ma). High scores on these scales suggest the presence of psychotic symptomatology, especially paranoid form (Gilberstadt and Duker 1965; Dahlstrom et al. 1972). Significant also in this regard is the fact that the modal MMPI profiles in this group by 1978 were 2-8-9 (31%) and 4-8-9 (14%), which are again indicative of psychotic symptoms.

The results of the psychological testing were mirrored by the results of the psychological interviews (table II) performed by the staff physician and psychologist at each readmission. These interviews in 1977-1978 indicated the presence of psychological symptomatology sufficient to warrant a primary or secondary psychiatric diagnosis in 71% of the subjects and referral to primary psychiatric treatment in 45% of the cases. The diagnosis of schizophrenia (Paranoid or Undifferentiated) was rendered in 63% of the cases and 8% were characterized as having sociopathic personalities. Seventy-two percent of the subjects reported visual or auditory hallucinations (during drug-free periods) and 18% suicidal ideation.

Group II - Psychodepressants - The group II subjects remained pri-

TABLE I

PSYCHOLOGICAL TESTING 1972-1978

	GROUP I PSYCHOSTIMULANTS		GROUP II PSYCHODEPRESSANTS		GROUP III NARCOTICS		BET. GROUPS SIG. IN 1973
	1972	1978	1972	1978	1972	1978	
N	11	11	14	14	26	26	
MEAN I.Q.	101	103	102	94*	104	102	+
MEAN C.Q.	93	94	93	81*	92	91	+
MMPI							
L	52	54	54	51	56	55	
F	64	96*	58	78*	62	66	*
K	56	58	53	58	51	56	
1. Hs	61	67+	61	72+	59	61	*
2. D	55	58	60	94*	60	66	*
3. Hy	60	71+	54	58	54	54	+
4. Pd	70	76+	68	74+	72	78	
5. Mf	64	70	60	58	68	66	
6. Pa	63	84*	57	55	59	61	*
7. Pt	56	57	58	62	58	62	
8. Sc	66	98*	60	63	64	61	+
9. Ma	64	87*	63	66	65	59	*
10. Si	48	55	55	59	56	58	
PREVIOUS PSYCH. TREATMENT	4%	63%*	0%	24%+	4%	8%	*

+ = $p \leq .05$
* = $p \leq .01$

TABLE II

ADMISSION STATUS 1978

	GROUP I PSYCHOSTIMULANTS		GROUP II PSYCHODEPRESSANTS		GROUP III NARCOTICS		BETWEEN GROUPS SIG.
N	11		14		26		
MAJOR DRUGS		%		%		%	
1st	Amphetamine	71	Barbiturates	82	Methadone	86	
2nd	Cocaine	41	Benzodiazepines	78	Synth. Opiate	59	
3rd	Phencyclidine	20	Alcohol	44	Heroin	52	
PSYCH. DIAGNOSES							
1st	Schiz. Paranoid	36	Dep. Neurosis	34	Psychopathic Personality	16	
2nd	Schiz.	27	Anxiety Reaction	21	Sociopathic Personality	12	
3rd	Undifferentiated Sociopath. Personality	8	Organic brain syn	14	Other	12	
ADMISSION SYMPTOMS		%		%		%	
Suicidal Ideation		18		77		16	*
Suicide Attempts		9		35		8	+
Hallucinations		72		6		8	*
Memory Change		9		35		4	+
Problems Concentrating		9		35		0	+
PERCENT REFERRED FOR PSYCHIATRIC TREATMENT		45		21		8	+

+ = $p < .05$
* = $p < .01$

marily psychodepressant users, although a significant proportion (34%) of these subjects reported abuse of alcohol instead of, or in addition to, barbiturate and benzodiazepine abuse.

Again, like the group I Psychostimulant users, the group II subjects evidenced significant changes in their psychological status by the 1978 admission. However, unlike the psychostimulant users, this group showed virtually no evidence of psychotic symptoms. As can be seen in the table I data, the most significant changes in the MMPI test results were found in the general pathology (F) and especially the depression (D) scales, although the entire group profiles were found to differ between 1972 and 1978 ($F=3.99$, df 1, 349, $p<.05$). Again, these testing results were reflected in the patients' 1977-1978 readmission symptoms, and in the diagnostic impressions of the admitting staff (table II). Anxiety and Depressive disorders were diagnosed in 55% of the group II subjects, and 21% were referred to primary inpatient psychiatric treatment. Especially significant is the fact that by 1978, fully 77% of this group reported suicidal ideations, and over 35% had actually attempted suicide. In addition, the incidence of drug overdoses was four times higher than in either of the other two groups.

Finally, the data from the Shipley Institute of Living Scale indicated a significant ($t=6.34$, df 13, $p<.001$) reduction in the mean conceptual quotient scores of this group between 1972 and 1978. Although this test provides only a rough index of conceptual impairment (i.e., brain damage), it is noteworthy that while all subjects in this group were within normal limits in 1972, and repeated administrations typically produce improved scores (Shipley 1940), fully 15% of this group showed worse results on the test and presumptive evidence of brain damage by 1978.

Group III - Narcotics - The subjects in group III remained primarily narcotic users with only slight evidence of regular nonopiate drug use. However, there was a clear shift in primary drug problems from heroin in 1972 to methadone (licit and illicit) and synthetic opiates by 1978. This shift may have been more a function of reduced quality and availability of heroin than a change in drug preference. An additional problem which was increasingly reported by this group is alcohol abuse. While only two subjects had changed their primary abuse problem to alcohol, all subjects had reported considerably greater day-to-day use of alcohol than at the time of their 1972 admission.

Results of psychological testing within this group indicated very low levels of symptom change, and no significant differences between years. Data from the 1978 SILS indicated no significant changes in group I.Q. or conceptual quotient (brain damage) scores, both of which were within normal population ranges (Shipley 1940; Simes and Simmons 1958). Similarly, results of personality testing with the MMPI showed no between-years effect ($F=1.06$, df 1,649, $p>.10$), and indicated only moderate levels of depression, and low levels of psychotic symptoms. Modal profiles for this group were comparable to those found in 1972; 2-4 (31%), 2-4-9 (11%), again suggesting

little systematic change in psychological status over the six year period.

Summaries of readmission interviews tended to support the results of the psychological testing. Comments from ward physicians and psychologists indicated a general group trend toward moderate increases in symptoms of depression, but little suggestion of psychotic symptomatology. By 1978, only two subjects had been referred for primary psychiatric treatment, both due to prominent suicidal ideation and recent attempts. Despite these two serious cases, the narcotic group generally showed the least change in psychological status over the six year period of drug use.

SUMMARY AND DISCUSSION

Two explanations are possible for the observed increases in psychological symptoms of groups I and II. First, it is possible that the patients in these groups may have already developed underlying symptoms of their subsequent disorders by 1972. While these symptoms were below the threshhold for detection at that time, they may have influenced the subjects' selection and pattern of drug use. That is, these patients may have required or responded preferentially to particular combinations of chemical agents due to the influence of their underlying symptoms. Thus, while these drugs did not prevent the subsequent expression of the disorders, they may have provided a particular form of relief. This "medication" view does explain the well documented (McLellan and Druley 1977; MacGahan and McLellan 1979; McLellan et al. 1979; Zuckerman et al. 1975; Smith and Fisher 1969) tendency for patients to select combinations of chemical agents having similar psychophysiological effects and to often reject other available types of drugs. This pattern of use suggests that many patients attempt to induce a particular effect, rather than simply "get high."

A second plausible explanation for the psychological symptom increases in groups I and II is that the prolonged abuse of the specific combination of street drugs had a direct role in the development and expression of the resulting disorders. This "developmental" view would suggest that while these subjects may have had undetected, borderline symptoms in 1972, and that they would have eventually developed a form of psychiatric illness regardless of drug use, the data presented here and elsewhere (McLellan and Druley 1977; MacGahan and McLellan 1979) argue that regular use of particular street drugs may hasten the development, and determine the nature of the subsequent disorder. The mechanism(s) by which the particular drug combination could determine the nature of a psychiatric disorder might include state dependent learning (Overton 1972) or even biochemical changes, through the prolonged alteration of CNS monoamine systems (Snyder 1972; Wyatt et al. 1972; Stein and Wise 1971). Regardless of the mechanism(s) involved, this view does suggest how many of the short term, toxic reactions to these drugs could develop the longer duration and manifestations of overt psychiatric syndromes following years of continued abuse.

If prolonged abuse of psychoactive chemical agents is associated with specific psychological disorders, then why are there no significant increases in psychological symptoms in the narcotics group? The answer to this question, we feel, lies in the specific psychopharmacological effects of the narcotic drugs. For example, in chemical structure morphine resembles the phenothiazine family (Goodman and Gillman 1965), and it has been used in this country (with some success) as an antipsychotic (Comfort 1977). It is our clinical impression that methadone, morphine, and to some extent heroin, may function to medicate underlying psychological problems, and to reduce symptoms of anxiety, depression, and paranoia.

Again, the data reported have been collected posthoc, on a relatively small sample of male, veteran drug abuse clients. Although the relationships reported are significant and distinct, the nature of the problem and the limitations of the data require continued, rigorous examination of this most intriguing area.

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Due to space constraints references are available from the senior author.

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Ethnoeconomical Approach to the Relationship Between Crime and Drug Use: Preliminary Findings

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Issues related to the economic behavior of narcotics addicts have never been satisfactorily resolved in the social scientific literature. This is because there has never been an adequate data base from which to address these issues. This paper constitutes a preliminary report on an attempt to construct such a data base.

The study has two principal foci; one substantive and the other methodological. The substantive focus is on the economic behavior of street level opiate addicts. Where does street addicts' income come from and where does it go? How much of that income comes from crime? How much of it is spent on drugs? The methodological focus revolves around the problems of trying to collect valid and reliable data on these issues. If addicts were able to accurately recall their income-producing and income-expending activities over long periods of time, then a retrospective interview type design would be adequate for collecting the sort of data that we are interested in. If, however, the ability of addicts to accurately recall their economic activities proved to be unreliable, then a different type of methodology would be required.

METHODOLOGY

Previous empirical research on the drug-crime relationship has mainly employed the survey approach among captive populations (i.e. those in prison or drug treatment facilities). Subjects in such studies engage in retrospective self-reporting that may span several decades. These studies have been essentially static in character, considering such variables as age of first drug use, age of first criminal activity, age of first arrest.

The intent of this study was to illuminate the processual aspects of the relationship between drug use and criminal activity. Ethnographic data collection techniques appeared best suited to this end. A storefront was rented, two indigenous field workers were hired, and information about the nature of our study was passed via word-of-mouth on the streets.

Once a subject had been recruited for the study he or she was given a Life History Interview (LHI). Each LHI session lasted one hour. Subjects typically received 2 or 3 LHI sessions. These had two principal purposes. The first was to engage in a protracted dialogue with respondents in order that we could get to know them and they could get to know us; in other words, to enhance feelings of trust and rapport.. The second purpose of the LHI sessions was to enable us to establish parameters of the sample. Basic demographic data (e.g. age, race), the prior nature and scope of subject's drug-using and criminalistic activities, employment histories, etc. were all recorded.

We also attempted to record subjects' economic behavior (i.e. all income and expenditures) for the year preceding the LHI. The results of this latter effort were disappointing. Few subjects were able to recall their economic activities for the prior year with any degree of accuracy. It was not uncommon for subjects to estimate expenditures 500 percent in excess of income. When this was pointed out to them they might reply, "Well, maybe I stole a lot more than I thought". Or, "Well, maybe I didn't use quite as much drugs as I thought". Or, "I don't know". Thus, while retrospective self-reporting may be an adequate technique for eliciting information about big events in subjects' lives (e.g. first heroin use, first arrest) it was inadequate for collecting data on the daily minutiae of everyday living that best express the routine on-going relationship between drug use and crime.

The core of our methodological approach thus became the daily follow-up of subjects. Subjects reported to the storefront 5 days a week and were debriefed on their previous days' activities in a 15-20 minute interview. Subjects were followed for at least 30 consecutive days and then replaced with new subjects from the pool who had already received life-history interviews.

About 50 percent of the subjects who began reporting on a daily basis completed the 30 day cycle. Three subjects were terminated because we learned they had broken into our storefront and stolen some tape recorders and typewriters. Several subjects failed to complete the thirty day cycle because of arrest and incarceration. Others just disappeared from the street and their whereabouts were unknown. This report is based upon the first eight subjects to complete the initial daily follow-up cycle. Table 1 provides some demographic data on these subjects.

Subjects' ages ranged from 24 to 39. Two were employed on a full time basis, one as a taxi driver and the other as a porter. Subjects had addiction histories besides heroin that included alcohol (n=2), methadone (n=1) and barbiturates (n=1). In addition, three subjects claimed that they had been addicted to cocaine.

TABLE 1

Demographic Characteristics of Research Subjects (N=8)

Mean Age:		32.5
Race:		
Hispanic	4	(50%)
Black	2	(25%)
White	2	(25%)
Employed full-time:		
Yes	2	(25%)
No	6	(75%)
Education:		
Some High School	4	(50%)
High School Grad	2	(25%)
Some College	2	(25%)
Mean Age of first Heroin use:		17.9
Addicted to Heroin:		
Yes	8	(100%)
Mean Number of Arrests:		5.6
Mean Number of Convictions:		1.5

FINDINGS

Income derived from criminal activity was the largest single category of cash income for the group, constituting 40 percent of total income. However, this is misleading in that a single subject, Steven H., accounted for about 65 percent of the group's total criminal income. In fact, Steven H.'s criminal income ($2,968) was more than 26 percent of the group's total income from all sources.

For all subjects the major portion of the category "Other Income" consisted of payments that they received from us for being research subjects. Only one of the 8 subjects received public support and this contributed negligibly toward his total income. Income from family, from wives or girlfriends, from public sources, from friends or from panhandling failed to contribute substantially to any subject's total income.

Most subjects were actively engaged in either legitimate employment or in criminal activity or in various aspects of the drug business. One half of the group earned more than 40 percent of their cash income through legitimate employment. Two subjects earned the majority of their income through legitimate employment. Three subjects earned 40 percent or more of their cash income from criminal activity, but only one subject earned the majority of his income in this manner. Only one subject reported no cash earnings from criminal activity.

TABLE 2

SUBJECTS' SOURCES OF CASH INCOME

Subject	Employment	Crime	Drug Business	Family	Wife or Girlfriend	Public Support	Friends	Other	Total Income
Steven H.	--	84%	1%	1%	--	6%	2%	6%	$3,522
Mike S.	42%	31%	--	1%	1%	--	5%	20%	$ 865
Keith D.	--	45%	25%	2%	5%	--	4%	19%	$ 850
Frenchy S.	7%	45%	11%	7%	3%	--	2%	25%	$ 795
Kerwin T.	59%	19%	3%	1%	--	--	3%	15%	$2,321
Keith H.	45%	8%	14%	1%	--	--	3%	29%	$1,198
Bobby H.	8%	7%	33%	5%	--	--	2%	45%	$ 475
Tito C.	76%	--	--	8%	1%	--	--	15%	$1,186
TOTAL	$3,270	$4,538	$728	$226	$75	$224	$267	$1,884	$11,212
	(29%)	(40%)	(7%)	(2%)	(0.6%)	(2%)	(2%)	(17%)	(100%)

Working within the drug business was the least important of the three major sources of cash income. Only 7 percent of the group's total cash income was raised in this fashion. One subject earned one-third of his income working in the drug business, and another earned one quarter. The remainder of the subjects earned little or no cash in this manner. However, many drug transactions involved pay-offs in drugs rather than in cash.

For 7 of the 8 subjects, more than 50 percent of their total expenditures involved the purchase of drugs. No subject reported any expenditures for gambling or legal fees. Less than half of the subjects reported expenditures for clothing, recreation (i.e. movies, ball games, shooting pool, discos, etc.) or savings. The expenditures that were reported in these categories, in all cases, were negligible. Subjects spent on the average about 6 percent of their cash income for food; 6 of the 8 subjects spent less than $1 per day on food, mainly as snacks. They obtained their main meal from mothers, girlfriends, or wives for no cash expenditure (table 3).

Expenditures for drugs clearly dominated the economic lives of these 8 subjects. Heroin was the principal drug used by respondents. Six of the eight subjects used more heroin (in terms of cash value) than any other drug. The predominant drug used by the remaining two subjects was cocaine. Only one subject consistently purchased less than half of the drugs that he consumed. Approximately 22 percent of the total amount of heroin consumed by the group was obtained as a gift or an in-kind payment.

Fluctuations in heroin consumption were far more pronounced in some subjects than in others. Table 4 reveals the mean dollar value of heroin used per day by each subject, the standard deviation of heroin use, and, also, the estimated daily dollar value of heroin that respondents reported during the LHI that they used for the previous year.

Several trends appear in table 4. The 4 subjects with the highest mean heroin use per day also have the highest standard deviations. Heroin addiction clearly is not the monolithic daily constant that some sources suggest. Heroin use by subjects in this group fluctuated considerably from day to day and it would be inaccurate to refer to them as $50/day or $30/day addicts. A similar situation was found in earlier research with prostitutes where it would be similarly inaccurate to refer to them as $100 call girls or $10 street hookers (see Goldstein, 1979). Prices for individual "tricks" were found to fluctuate widely. References to addicts as having specific dollars-per-day habits, or to prostitutes as having specific dollars-per-trick fees, are part of an everyday verbal shorthand that make our perception of the world simpler and make "reality" easier to grasp. But it must be remembered that this conceptual shorthand simplifies reality, and in doing so obscures the many complexities that characterize reality.

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TABLE 3

SUBJECTS' CASH EXPENDITURES

SUBJECT	TOTAL EXPENDITURES	DRUGS	ALCOHOL	LIVING[1]	FOOD	FAMILY	CLOTHING	CIGARETTES	OTHER
Steven H.	$3,732	83%	-0-	2%	7%	4%	-0-	2%	2%
Mike S.	$ 826	59%	6%	-0-	6%	16%	-0-	2%	10%
Keith D.	$ 851	90%	3%	-0-	3%	3%	-0-	1%	1%
Frenchy S.	$ 827	86%	1%	-0-	7%	-0-	-0-	1%	5%
Kerwin T.	$2,304	65%	4%	21%	6%	-0-	-0-	1%	3%
Keith H.	$1,272	53%	5%	9%	9%	-0-	3%	3%	18%
Bobby H.	$ 540	23%	14%	-0-	5%	36%	4%	5%	13%
Tito C.	$1,093	74%	-0-	-0-	5%	12%	-0-	1%	8%

1. Includes rent, utilities, telephone, etc.

TABLE 4

SUBJECT'S HEROIN USE			
Subject	Mean Dollar Value of Heroin Use per Day	Standard Deviation	Estimated Heroin Use For Previous Year
Steven H.	$49	18.52	$60
Mike S.	13	11.74	50
Keith D.	32	22.42	50
Frenchy D.	25	19.64	60
Kerwin T.	11	9.32	30
Keith H.	8	10.44	Information not available
Bobby H.	9	8.66	10
Tito C.	20	25.47	100

All 7 of the subjects for whom complete data were available estimated their average daily heroin use for the previous year to be higher than what was found in the current daily follow-up. The average mean daily cost of heroin use reported on our daily follow-up was $22.7 per day. However, the same 7 subjects estimated their average daily heroin cost for the previous year to be $51.4 per day. While it is possible that each subject used less heroin this year than last year, we believe that these data indicate that our daily follow-up technique is eliciting more accurate data than is gathered through the more typical method of doing a single interview with a subject and asking him to recall specific activities occuring over extended periods of time.

The daily follow up of narcotic addicts has enabled us to produce economic data with a clarity, richness and depth not previously available. It appears clearly superior to data gathered via retrospective interview techniques. This paper constitutes only the preliminary analysis of the first group to complete the daily reporting cycle. As the number of cases accumulate, we should be able to typologize addicts according to their economic lifestyle and to utilize that typology for purposes of hypothesis testing and theory building.

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The Impact of Heroin Addiction Upon Criminality

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STATEMENT OF THE PROBLEM

There is rather general agreement among criminologists that an increase in criminality commonly occurs following the onset of heroin addiction in the United States (Chein et al. 1964; O'Donnell, 1966 and 1969; Ball and Snarr, 1969; Nash, 1973; McGlothlin, Anglin and Wilson, 1978). Despite this overall consensus, however, the dynamics of the relationship between opiate addiction and crime continues to be a matter of controversy. Among the questions which remain unresolved, two seem especially crucial: (1) What are the frequency and types of crimes committed by heroin addicts? (2) What impact do post-onset periods of heroin addiction or periods of abstinence have upon criminality?

A NEW MEASURE OF CRIMINAL BEHAVIOR

In the present paper, a new measure of criminal behavior is described and employed in an on-going research project. The new measure has been termed Crime-Days Per Year At Risk. A crime-day is a 24 hour period in which an individual commits one or more crimes. The number of crime-days per year at risk refers to the number of days per year that an individual has committed crimes, from 0 to 365. Years at risk refers to time when the subject was not incarcerated; risk is time "on the street".

This new measure, crime-days per year at risk, is found to have unique analytical power as it permits the calculation of uniform crime rates by years at risk and it is not confounded by multiple crimes committed on a given day. Furthermore, the term crime-days per year at risk appears to be an effective procedure for explaining and understanding the extent of persistent criminal behavior because it relates the number of crimes committed by individuals to a common frame of reference -- times per year. The discovery of the average crime-days per year concept was

made by the senior author while analyzing detailed life history data pertaining to heroin addicts as part of an on-going follow-up study in Baltimore.

THE SAMPLE OF ADDICTS

This paper is based on interview data obtained from 243 Baltimore opiate addicts (most were heroin addicts). The 243 male addicts were a stratified random sample drawn from 4,069 persons listed by the Baltimore Police Department between 1952 and 1971 as known addicts. Analysis of cohort and race differences has been undertaken elsewhere (Nurco and DuPont, 1977).

Although comprehensive institutional data was collected with respect to the addict sample, the main source of data for the present analysis was obtained through personal interviews. Each of the 243 addicts was interviewed during 1973 or 1974 by specially trained interviewers who were familiar with the Baltimore addict subculture. The interview lasted some three hours and the questions were focused upon six topics: drug use, criminal behavior, work, living arrangements, drug selling and other sources of income. The validity of the interview data was found to be satisfactory in a separate study (Bonito, Nurco and Shaffer, 1976).

ADDICTION STATUS AND CRIMINALITY SINCE ONSET

After the number of crime-days since the onset of regular opiate use had been coded for each subject, it was possible to classify both his addiction status and criminality during his years at risk. Thus, the following data was coded for each subject: (1) total crime-days while addicted, (2) total crime-days off opiates while "on the street", (3) crimeless days while addicted and (4) crimeless days while off regular opiate use. These four statuses were mutually exclusive.

For the entire sample, the most frequent addiction-crime status during their entire risk years was that of being addicted and committing crimes on a daily basis; this occurred during 41.7 percent of the risk period (Table 1). Next most common was being off regular opiates and not committing daily crimes; this occurred for 34.5 percent of the risk period. The remainder of the risk period was accounted for by addicted time when crimes were not committed (19.9 percent) and abstinent time when crimes were committed (3.9 percent of days).

TABLE 1 Total Time at Risk by Addiction Status and Criminality for 237 Addicts

Status While At Risk	Days in Each Status	Percent of Days in Each Status
1. Crime-Days on Opiates	432,947	41.7
2. Crime-Days off Opiates	40,791	3.9
3. Crimeless Days on Opiates	206,082	19.9
4. Crimeless Days off Opiates	358,304	34.5
Total Days at Risk:	1,038,124	100.0

The total amount of time that this Baltimore male sample spent addicted to opiate drugs since onset of regular opiate use was 61.6 percent of their risk years. Since their average years at risk was 11.3, they were addicted to opiates almost two-thirds of the time and abstinent somewhat over a third of the time. Two further points are pertinent about their addiction or abstinence status. First, with regard to the abstinence from regular opiate use classification, this status included periods of occasional use of opiates as well as periods of frequent use of non-opiate drugs. Second, it is significant that 85 percent of the sample had such abstinence periods.

NUMBER OF CRIMES COMMITTED BY THE 243 ADDICTS

The total number of crime-days during the risk years for the 243 addicts is tabulated in Table 2. The range in crime-days within the sample was from 0 to 9,450. That is, from no crimes committed by six addicts to 9,450 crime-days accumulated by one addict during his risk years.

The total number of crime-days amassed by these 243 addicts during their years at risk was 473,738. This total may be regarded as an underestimate of the total number of crimes committed, as multiple crimes during a crime-day were common. It is also pertinent to note in this context that most of the crimes reported were for theft and that drug use or possession was not classified as a crime. The mean number of crime-days per addict during their years at risk was 1,998.9.

TABLE 2 Total Crime Days for 243 Addicts

Crime Days	Number of Addicts	Percent of Addicts
0 (None)	6	2.5
1-99	20	8.2
100-499	31	12.8
500-999	31	12.8
1,000-1,999	54	22.2
2,000-2,999	46	18.9
3,000-3,999	27	11.1
4,000-4,999	12	4.9
5,000-5,999	10	4.1
6,000-9,450	6	2.5
Total	243	100.0

Total crime-days since onset of addiction: 473,738

In order to control for years at risk, crime-days were computed for each person by years at risk (Table 3). This measure - Crime-Days Per Year At Risk - indicates the average number of crime-days per year during the risk years for each of the 243 addicts. The mean number of Crime-Days Per Year At Risk for the sample was 178.5. Thus, the total amount of time that these addicts spent engaged in daily criminal behavior since their onset of addiction was almost half of their risk years. To be exact, they committed crimes during 45.6 percent of their days at risk.

TABLE 3 Crime-Days Per Year at Risk for 243 Addicts

Crime-Days Per Year at Risk	Number of Addicts	Percent of Addicts
No Crime-Days	6	2.5
Less than 1 per yr.	11	4.5
1-49	35	14.4
50-99	26	10.7
100-149	31	12.8
150-199	32	13.2
200-249	25	10.3
250-299	26	10.7
300-349	28	11.5
350-365	23	9.5
Total	243	100.0

THE IMPACT OF ADDICTION UPON CRIMINAL CAREERS

Each of the 243 addicts was classified as to the common criminal career which he had followed since onset of regular opiate use (Table 4). The extent of criminality among all nine career types was affected by their addiction status. Thus, there was an overall six-fold increase in the number of crime-days per year during addiction as contrasted with the crime rate when abstinent.

Although the extent of criminality within this addict sample was notably increased when the subjects were addicted to opiate drugs, the non-addicted crime rate was still quite high. Thus, two of the career types had more than 100 crime-days per year while not addicted to opiates.

TABLE 4 Crime-Days Per Year At Risk By Addiction Status

Crime Career Type	Number of Addicts	Crime-Days Per Year at Risk	Crime-Days Per Year at Risk: addicted	abstinent
1. Theft-daily	41	330.3	347.7	109.7
2. Sale of Drugs-daily	13	328.0	353.2	88.3
3. Other Crimes-daily	7	319.4	341.4	151.0
4. Weekly Theft	58	189.6	280.9	23.3
5. Weekly Sale of Drugs	18	181.1	284.0	27.6
6. Weekly, other crimes	7	201.9	297.0	70.1
7. Infrequent Theft	57	72.4	140.7	7.4
8. Infrequent Sales	14	102.4	260.9	10.5
9. Infrequent, other crimes	22	46.8	108.2	2.3
No Crime	6	---	---	---
Total:	243	178.5	248.0	40.8

INTERPRETATION AND CONCLUSION

In this study of male heroin addicts in Baltimore, it has been found that most of the subjects were deeply enmeshed in criminal careers on a daily basis over a period of many years. Secondly, it has been found that the vast majority of these crimes were committed while the subjects were addicted to opiates. Conversely, the rate of criminal activity was greatly reduced when these subjects were abstinent.

With respect to criminality, it was found that each of the 243 addicts committed an average of 1,999 crimes (i.e. had 1,999 crime-days) and that together this sample was responsible for committing at least 473,738 offenses. (These figures do not include drug use or drug possession offenses). On an annual basis, this sample of male addicts committed 178 crimes per year since their onset of regular opiate use.

The association of this high level of criminal behavior with active addiction to opiates was striking. Thus, the rate of criminal offenses committed increased six times during their addiction periods as contrasted with their abstinence periods. With respect to years at risk, 91.4 percent of their crime-days were also days during which the subjects were addicted; conversely, only 8.6 percent of their crime-days were abstinent days.

These research findings concerning the impact of addiction upon criminality are consistent with those of various other studies. (Sutter, 1966; Ball and Snarr, 1969; Preble and Casey, 1969; DeLeon et al. 1972; Inciardi and Chambers, 1972; Nash, 1973). At the same time, employment of a new measure of criminality (crime-days per year at risk) provides a more meaningful and statistically valid procedure for analyzing the crime-drug relationship than has previously been available. For it is now feasible to compare rates of criminality and relate these differential rates to various aspects of drug addiction.

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Drug Abusers: Defeated and Joyless

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INTRODUCTION

It has long been recognized that individuals who abuse one psychoactive drug are likely to abuse others. Such an association is especially strong between opiates and sedative-hypnotics, including alcohol. It is our thesis that this indiscriminate urge to take drugs is supported (and possibly initiated) by a common drug effect that improves feelings and/or produces amnesia for unpleasant feelings.

This study is an extension of a new approach to identifying pathological feeling states in alcohol and opiate abusers. Martin, Hewett, Baker, and Haertzen (1977) postulated that alcoholics and opiate addicts are characterized by high basic needs, impulsivity, egocentricity, sociopathy, and hypophoria. Various definitions of hypophoria have included elements of lack of confidence, low energy, joylessness, and self-perceived unpopularity. Martin, Haertzen, and Hewett (1978) hypothesized that hypophoria was a feeling state that occurred with increased frequency or intensity in drug abusers. Since trait measures such as the MMPI or ARCI psychopathy scales were known to be insensitive to acute drug effects or withdrawal from drugs, new instruments with a more current time frame were developed. Martin et al. (1977) devised a short questionnaire (Maturity Scale) which contains rationally derived subscales to measure five of the characteristics which they postulated for drug abusers. Haertzen, Martin, Hewett, and Sandquist (1978) constructed a long instrument, The Social Experience Questionnaire (SOEX), and then short psychopathic state scales (Haertzen et al., in press).

This study is concerned with describing more precisely the pathological feelings common to many alcoholics and opiate addicts. The rather broad focus of Martin's initial conceptualization of hypophoria led us to hypothesize that such a feeling state might consist of more than one independent component. Accordingly, in Experiment I we reanalyzed the data from the SOEX, starting with new, rationally constructed marker scales for four components of hypophoria: lack of confidence, low energy, joylessness, and unpopularity.

EXPERIMENT 1

Methods

Subjects

Three male groups were studied: Control subjects (n = 54) consisted of students, faculty, and staff from a religious college and seminary. Participation was restricted to those who had never been treated for alcohol or drug problems. Alcoholic subjects (n = 53) had been treated for alcoholism by an agency in the Lexington area. Opiate addicts (n = 28) were Federal prisoners with a documented history of repeated opiate use who had volunteered for studies at the Addiction Research Center.

Data Analysis

LONG SCALES: Initial rational scales were derived from the SOEX items by using the judgment of two raters. Four long scales resulted: Lack of Confidence, Low Energy, Unpopularity, and Joyless. There were high correlations (all but one above .45) between the long Lack of Confidence, Unpopularity, and Low Energy scales. However, none of these scales were strongly related to the Joyless scale. The 128 items of three correlated scales were therefore combined into a scale labeled Defeated. Overlapping items that could be appropriate to both the Joyless and Defeated scales were eliminated. These two scales were then scored and intercorrelated in the three criterion groups. Their correlation was significantly positive: r = .201; ($.01 < p < .05$).

SHORT SCALES: Two short scales were selected from the items that were originally members of the long Defeated or of the long Joyless scales. Basically, the 15 items with the largest correlations between that item score and the appropriate long scale were selected. All items on the short Defeated scale marked true are scored positively. In contrast, the Joyless scale measures denial of positive feelings. It is a euphoria scale with the items scored positively when the answers are false. These scales are available from the authors upon request.

Results

SHORT SCALES: The 15-item Defeated and Joyless scales produce patterns that are similar to the long scales. Each short scale correlates strongly with its parent long scale, .865 and .953, respectively, but is slightly less powerful in differentiating the three clinical groups. The correlation between these two short scales is not significant in these population samples.

The short Defeated scale clearly segregates alcoholics from normals ($p < 10^{-6}$) and addicts from normals ($p < 10^{-9}$), but the two drug-abusing groups do not differ significantly. The possible diagnostic usefulness of this scale is indicated by the fact that if a cutoff score of 5 (T score = 59.05) is established, none of the

normals' scores exceed this level. However, 41.5% (n = 22) of the alcoholics and 57.1% (n = 16) of the addicts had scores above this limit.

The short Joyless scale does not distinguish between alcoholics and normals, but does differentiate addicts from both alcoholics (p = .0018) and normals ($p < 10^{-5}$).

HYPOPHORIA SCALE: The 15-item Hypophoria scale developed by Haertzen et al. (1979) from the SOEX appears to combine aspects of both the Defeated and Joyless scales. Hypophoria correlates significantly with both these scales (.680 and .406, respectively). It clearly differentiates alcoholics from both addicts (p = .00015) and normals ($p = 10^{-6}$).

The Defeated and Joyless scales were derived from differences between criterion groups, whereas ARC Inventory scales were validated using drug-induced states. In order to establish that both types of measures are also senstiive to naturally occurring changes in feelings, Experiment 2 was conducted.

EXPERIMENT 2

Methods

College students, 24 men and 24 women, participated in Experiment 2 for credit in an introductory psychology course. As part of a larger study, the subjects were shown the TV film Christmas in Appalachia. The extent of the change in their feelings was measured by two tests, the Profile on Mood States (POMS) and the Present Affect Rating (PAR), given before and after the film.

Instruments

POMS: This instrument contains 65 adjectives relating to feelings, and is divided into six scales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor, Fatigue, and Confusion-Bewilderment. The subjects were asked to rate adjectives on an intensity scale ranging from 0 ("not at all") to 4 ("extremely"). Raw scale scores were calculated by adding these item ratings.

PAR: This test consists of 106 sentences relating to feelings, attitudes, and opinions. Short (14-17 items) versions of four drug-effect scales from the ARC Inventory were included: the Morphine-Benzedrine Group (MBG), Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), LSD, and Tired scales. The other four scales on the PAR were derived from the SOEX that was used in Experiment 1. The short scales for Hypophoria and Sociopathy, as well as Defeated and Joyless, were utilized to sample a range of feelings and attitudes possibly associated with addiction and psychopathic states.

Each subject responded to PAR items by using one of four responses: strongly agree, mildly agree, mildly disagree, or strongly disagree,

and these responses were numerically weighted. Raw scale scores were calculated by adding these weighted items.

FILM: Christmas in Appalachia is a half-hour black and white movie that was originally broadcast as a CBS News Special Report in the mid-1960s. Charles Kuralt narrates his visit to a small community in the mountains of southeastern Kentucky. Extreme poverty is evident in all the families of unemployed coal miners that Kuralt interviews. The celebration of Christmas only serves to emphasize their sadness, unhappiness, futility, and despair.

Procedures

The subjects completed the POMS and the PAR before the film (Test 1). Immediately after the film, the participants again completed the POMS and PAR (Test 2) with respect to their feelings during the film. To permit the scores on the various scales to be compared with one another, the raw scores were converted to standardized T scores with a mean of 50 and a standard deviation of 10, by using the means and standard deviations for the pre-film test as the basis of adjustment.

Results

Film Effects

The effects of the film on feelings varied greatly (Table 1). The largest effect was an increase in Depression-Dejection, $p = 2 \times 10^{-6}$ (two-tailed). Changes on four interrelated scales were also highly significant: increases in Joyless ($p = .0001$) and Hypophoria ($p = .0008$), and decreases in Vigor ($p = .00001$) and MBG ($p = .0002$). In contrast, no significant changes were produced in Defeated or Fatigue; there was a relatively small (though significant) increase in Confusion-Bewilderment ($p = .017$). The difference between the large increase in Joyless and the small change in Defeated was significant ($p = .0089$).

So, despite the fact that the film depicted a number of defeated people, the Defeated scale was not significantly elevated in the college students who watched it. In contrast, scores on the Joyless scale were strongly increased. It is apparent that the Defeated scale is more stable, requiring a more intense stimulus or more personal involvement than that provided by the poverty film to change this aspect of these nonaddict subjects.

DISCUSSION

Hypophoria

Both experiments in this study demonstrate that two separate components, Joyless and Defeated, can be identified which were previously subsumed within Martin et al's. (1977) concept of hypophoria.

Joyless

The data from Experiment 1 suggest that joyless feelings may be a component of a pathological state that is greater in opiate addicts. Experiment 2 found that the Joyless scale is strongly and inversely correlated with the MBG scale, a well-validated measure of euphoria induced by the opioids and other drugs of abuse. This finding is consistent with the idea that opioids may be used to relieve feelings of joylessness. However, the greater Joyless feelings in addicts may also be due to the fact that they were prisoners, while the other groups were not.

Defeated

Defeated appears to be particularly important in understanding pathological feeling states, since it differentiates both alcohol and opiate abusers from normals. Prior explanations of antisocial behavior might be related to defeated feelings: for example, anomie, hopelessness, alienation and apathy. Several previous studies support the idea that drug abusers have low self-esteem (Vanderpool, 1969; Berg, 1971). It is noteworthy that there is no substantial correlation between Tension-Anxiety and Defeated in Experiment 2. This would suggest that prior equivocal experimental data regarding tension-reduction models of alcoholism are not necessarily related to hypotheses about feelings of defeat in drug abusers.

Psychopathic State

We think that drug abusers might suffer from some distinctive pattern of pathologic feelings--particularly defeated ones--which can lead to and/or result from chronic drug intake. This has been termed a psychopathic state, to differentiate it from a stable psychopathic trait. It is not yet clear whether feelings of defeat or other elements of a psychopathic state are relatively constant, or if they occur in episodes similar to anxiety (or panic) states. This underlying disease process, or psychopathic state, may occur in drug abusers even when they are not using drugs.

Drugs and Defeated Feelings

Psychoactive drugs (for example, alcohol and opioids) may be used to relieve persistent or episodic feelings of defeat. Several studies in which the experimental manipulation threatened the subject's self-image produced an increase in alcohol consumption (Nathan and Lisman, 1976). Although two studies report that drinking alcohol directly improves the current self-concept of alcoholics (Berg, 1971), three others do not support this conclusion (Pollack, 1965; Vanderpool, 1969; Vanicelli, 1972).

Drugs that counteract feelings of defeat do not necessarily have to do so by producing opposite feelings, such as success; aiding the users to forget or suppress from consciousness the unwanted feelings may be quite sufficient to provide relief. Both alcohol

(Cowan, 1978) and marijuana (Cowan, Neidert, and Miller, in preparation) produce an amnesia for feelings of Fatigue and Confusion. These POMS scales were related to the Defeated scale in Experiment 2. It would, therefore, appear profitable to test psychoactive drugs for their ability to induce amnesia for defeated feelings.

One can, then, generate viable hypotheses which specify that some psychoactive drugs act to produce amnesia for defeated feelings, to suppress their episodic occurrence, or to temporarily counteract them. These hypotheses could account for the repetitive use of drugs such as alcohol or heroin, even though there is considerable evidence that these drugs do not produce consistently euphoric states. Instruments such as the Defeated and Joyless scales may prove of value in the assessment of the underlying disease process in drug abusers, and its modification by the efforts of treatment programs.

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TABLE 1

Changes in Feelings Produced by the Film(a)

Mood Scale	Mean Raw Scores		T score difference
	Pre-Film	Post-Film	
POMS(b):			
Tension-Anxiety	8.62	7.48	-2.28
Depression-Dejection	7.08	13.35	+8.81****
Anger-Hostility	5.13	7.92	+5.37***
Vigor	15.31	11.65	-5.91****
Fatigue	6.27	6.92	+1.21
Confusion-Bewilderment	7.08	7.87	+2.34*
ARCI(c):			
MBG(e)	21.85	18.04	-5.29***
PCAG(f)	20.31	22.23	+2.83**
LSD	13.58	14.98	+2.71*
Tired	26.67	29.31	+4.06***
SOEX(d):			
Defeated	19.58	20.27	+1.14
Joyless	22.15	25.94	+4.88****
Hypophoria	17.73	20.42	+4.09***
Sociopathy	12.83	12.69	+0.28

(a) A positive difference indicates that the film increased the average intensity of that feeling in the 48 subjects (T scores).
(b) Scales from the Profile on Mood States (POMS).
(c) Scales on the Present Affect Rating (PAR) derived from the Addiction Research Center Inventory (ARCI).
(d) Scales on the PAR derived from the Social Experience Questionnaire (SOEX).
(e) Morphine-Benzedrine-Group scale.
(f) Pentobarbital-Chlorpromazine-Alcohol-Group scale.

*$p < .05$ (Two-tailed t test); **$p < .01$; ***$p < .001$; ****$p < .0001$.

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Outpatient Treatment and Outcome of Prescription Drug Abuse

Tennant, F. S., Jr.

SUMMARY-ABSTRACT [1]

Forty-six consecutive patients who voluntarily sought outpatient treatment for abuse of one or more prescription drugs were studied. Barbiturates, amphetamines, and diazepam were the most common drugs abused. Desired treatments by patients included counseling, medical withdrawal, or medical maintenance with the drug of abuse or a chemically related drug. Twenty-two (47.8 percent) patients left treatment and relapsed within one month; another eight (17.4 percent) patients relapsed between one and three months after entering treatment. Only 13 (28.3 percent) reported abstinence 90 days after entering treatment. This experience suggests that a wide range of medical, social, and psychologic resources are required to treat prescription drug abuse, and that long-term drug abstinence is difficult to achieve with all patients.

INTRODUCTION

Treatment of prescription drug abuse has dealt primarily with drug complications such as overdose, toxic reactions, and techniques for medical withdrawal.[1-5] Other reports describe behavior patterns of prescription drug abuse and often refer to it as polydrug abuse, since many persons frequently abuse more than one drug.[6-8] Some reports emphasize the clinical complexity of polydrug abuse and particularly note the severity of multiple medical and psychiatric complications.[9-11] Few attempts have been made to describe treatment and outcome of prescription drug abuse.[12] Reported here is a series of 46 consecutive patients who voluntarily sought outpatient treatment for prescription drug abuse. Type of treatment desired, concomitant medical and psychiatric conditions, treatment given, and outcome are described.

METHODS

Forty-six consecutive patients voluntarily sought outpatient treatment for prescription drug abuse between January 1 and June 30, 1977. All patients stated that they used their prescribed drug(s)

compulsively one or more times a day for at least 60 days. When admitted, a patient's complete history was taken and a physical examination was done, including necessary laboratory and urine drug-screening procedures.[13] Part of the history taking included a written checklist of the following psychiatric symptoms and conditions: anxiety, depression, hallucinations, insomnia, and nervousness. Patients also completed, in writing, the following questions that were answered yes or no to help screen for psychosis and suicidal thoughts:

I am depressed at this time.
Have you ever tried to commit suicide?
Right now I feel as though I want to injure myself or someone else.
Right now I feel I do not particularly want to live.
I sometimes hear noises or see things that aren't really there.
I sometimes think that part of my body disconnects and leaves for a short time.
I sometimes think I do not have total control over my mind.
I think that most of the people I know are against me.

Depression and suicidal tendency were further assessed and documented by an elevated score (above 16 on a scale of 0 to 39) on the Beck Depression Inventory.[14] No patients were admitted to the study who exhibited evidence of delirium, intoxication, or dementia. Patients were specifically asked the reason the drugs were prescribed, which drug(s) they used, and whether they perceived an adverse drug effect on health, mind, work, social function, and marriage, or whether they were physically addicted to their drug(s). The patients were also asked the type of treatment(s) desired, including medical withdrawal, counseling, or medical maintenance with the same drug or one chemically related to it. Following intake procedures, the patient was assigned to an experienced drug treatment team that consisted of a physician, registered nurse, psychiatric technician, and licensed marriage and family counselor.

If the patient desired medical withdrawal, a medical detoxification regimen was prescribed, which usually required that the patient attend clinic on a daily basis. Although amphetamines and methylphenidate hydrochloride do not apparently cause physical dependence, some patients requested medical withdrawal for dependence on these drugs; this was provided.[2] The following drugs were used for detoxification and withdrawal purposes: hydroxyzine pamoate for barbiturate or other sedative-hypnotic dependence; hydroxyzine for amphetamine or methylphenidate dependence; and propoxyphene napsylate or diphenoxylate hydrochloride for codeine, pentazocine hydrochloride, oxycodone hydrochloride, and propoxyphene hydrochloride dependence. Hydroxyzine was chosen as a withdrawal agent since it is a sedative with antihistamine properties that has low abuse and overdose potential, and it has been found effective in alcohol withdrawal.[15-17] Propoxyphene napsylate and diphenoxylate were chosen because they are compounds with relatively low abuse potential that can effectively suppress narcotic withdrawal.[18-22] Withdrawal agents were administered in a declining dose fashion over a two- to three-week period. Following detoxification, each patient entered an ongoing counseling program in which the patient attended the clinic at least once a week. Counseling sessions

lasted 15 to 45 minutes and were primarily supportive in nature, with attention particularly directed at the patient's marital, employment, health, or financial problems. Special focus was directed on guiding the patient to find alternatives to taking a prescribed drug(s) when he/she experienced a symptom such as nervousness, lethargy, or depression, although no specific relaxation technique such as biofeedback, hypnosis, or meditation was used. Sessions often included family members, and they were continued weekly until the patient dropped out of treatment. Medical maintenance was done by substituting a drug chemically related to the one of abuse. It was done when the patient desired it and when no treatment alternative was deemed viable. Each patient was interviewed by telephone or by face-to-face contact approximately 90 days after admission to solicit a self-report and determine outcome. Longer follow-up was obtained for patients who remained in treatment more than 90 days.

RESULTS

Most patients were under age 27 years (mean, 26.1 years). There were a few more men (25 of 46 or 53.3 percent) than women. The majority were neither married nor employed (Table 1). Most patients (34 or 73.9 percent) desired counseling (6 or 13.0 percent) for treatment, although others requested medical withdrawal (11 or 23.9 percent) or medical maintenance (6 or 13.0 percent) with the same or related drug. Some patients wanted more than one type of treatment. The most common drugs of complaint were barbiturates, amphetamines, and diazepam (Table 1). Patients stated they had used their drugs from one to 14 years, with a mean of 4.5 years. Some patients used more than one drug obtained by prescription. Every patient stated that he used his drugs in excess to what was prescribed by his physician. Patients had usually obtained their drugs for depression, insomnia, anxiety, "nervousness," weight control, or minor pain problems such as headache. All patients except one perceived that their drug use had developed into a "problem" and had an adverse effect on their mind, health, social and work functions, marriage, or that they were addicted (Table 2). These patients had numerous medical and psychiatric complaints. Anxiety or nervousness, depression, insomnia, chronic pain, suicidal thoughts, and obesity were the most common (Table 3).

Twenty-two (47.8 percent) patients left treatment within one month and reported relapse at 90-day followup (Table 4). Eight (17.4 percent) patients left treatment between one and three months and relapsed. Thirteen (28.3 percent) patients remained in treatment and reported abstinence at 90-day followup. Urine that did not contain a detectable, abusable drug was obtained from these patients and supported their claim of abstinence. Two of the 13 patients relapsed, however, shortly after the 90-day followup. Six (13.0 percent) patients requested medical maintenance with their chosen drug of abuse or a chemically-related drug, and this was provided in four of these patients. Three of the four were still in maintenance treatment at the 90-day followup. One patient relapsed shortly after three months, one continued maintenance after one year, and one achieved abstinence after almost one year of maintenance.

COMMENT

The patients studied here excessively abused one or more prescribed drug and volunteered for treatment. None was referred by the judicial system for mandatory treatment, which is frequently done with casual drug users.[10] Patients perceived that prescribed drugs had a variety of adverse effects when used to excess. The three predominant treatments requested were counseling, medical withdrawal, and medical maintenance with their drugs of abuse or chemically-related drugs. Patients had many medical and psychiatric complaints and conditions, as has been previously reported with groups of polydrug abusers.[9-11] The numerous medical and psychiatric conditons, variety of drugs abused, and different forms of treatment desired by these patients made treatment a complex endeavor that required a well-trained, multidisciplinary clinical team with considerable clinical resources. All patients were similar in that they knowingly exceeded the prescribed dosages intended by the initial prescribing physician.

Anderson et al. attempted to treat a group of patients with amphetamine, barbiturate, and hallucinogen problems on an outpatient basis and encountered dismal treatment outcomes. Only eight of their 83 patients even returned for a second clinic visit.[12] Outcome in the patients studied here appeared better in that patients almost always returned to the clinic for followup treatment visits, but only 13 of 46 (28.3%) reported abstinence 90 days after entering treatment. A different treatment program that uses more frequent counseling, medical maintenance, or other techniques may have improved outcome. If patients had been mandated by the judicial system to accept treatment in lieu of incarceration, treatment outcome may have been better.[25] Although medical maintenance with methadone is an accepted treatment for heroin addiction, the concept of medical maintenance for prescription drug abuse has not been well explored. Six of 46 (13%) patients specifically requested this form of treatment, which suggests that this approach to prescription drug abuse deserves further study. Despite difficulty in achieving long-term abstinence with most outpatients studied here, there is no reason to conclude that inpatient treatment would have produced better outcome.

TABLE 1. Drugs of Complaint Among 46 Prescription Drug Abusers

	No. of Patients*	%
Barbiturates	19	41.3
Amphetamines	18	39.1
Diazepam	10	21.7

*Total is more than 46 since some patients complained about more than one drug.

Codeine	3	6.5
Methaqualone	3	6.5
Propoxyphene hydrochloride	3	6.5
Pentazocine	2	4.3
Methylphenidate	1	2.2
Chlordiazepoxide	1	2.2
Meprobamate	1	2.2
Oxycodone	1	2.2

TABLE 2. Patients' Perceptions of Adverse Drug Effects

	No. of Patients*	%
Work/social function	24	52.2
Health	19	41.3
Mind	15	32.6
Physically addicted	7	15.2
Marriage	3	6.5
No adverse effects	1	2.2

*Total is more than 46 since some patients perceived that drug use had multiple adverse effects.

TABLE 3. Psychiatric-Medical Complaints and Problems Found in 46 Prescription Drug Abusers

	No. of Patients*	%
Anxiety or nervousness**	35	76.1
Depression** +	25	54.3
Insomnia	24	52.2
Chronic pain	8	17.4
Suicidal thoughts	7	15.2
Obesity	4	8.7
Seizure disorder	2	4.3
Psychotic disorder	1	2.2
Arteriosclerotic heart disease	1	2.2
Congestive heart failure	1	2.2
Hypertension	1	2.2
Regional Enteritis	1	2.2
Thyroid nodule	1	2.2
Endometriosis	1	2.2
Peptic ulcer	1	2.2
Amenorrhea	1	2.2

*Total is more than 46 since some patients had more than one complaint or problem.
**Presence based on patient self report and/or screening questionnaire.
+Presence based on screening questionnaire and Beck Depression Inventory.[14]

TABLE 4. Outcome of Treatment

	No. of Patients	%
Left treatment within 1 mo. and reported relapse at 90-day followup	22	47.8
Left treatment between 1 and 3 mo. and reported relapse at 90-day followup	8	17.4
Remained in treatment and reported abstinence at 90-day followup	13	28.3
Medical maintenance over 90 days	3	6.5
Totals	46	100

Nonproprietary Name and Trademarks of Drug

Methaqualone - Quaalude, Sopor, Tuazole.

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FOOTNOTE

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Addicts and Drugs

Nurco, D. N.; Wegner, N.

This paper, a retrospective study in the anthropological oral-history tradition, presents an overview of drug addiction in Baltimore City from 1950 through 1977. Interviews were conducted with male addicts and ex-addicts who served as research informants to describe the conditions prevailing on the narcotic drug scene in Baltimore during that period. Each addict was considered as a participant observer, and the interview focused on his observations of the conditions that prevailed in Baltimore during his periods of addiction and not upon his own activities or habits. In addition to the interviews, data were drawn from available police statistics and from the Maryland State Drug Abuse Administration.

METHODOLOGY

The formal design of the sample of addict informants called for the selection of persons who could report on two or more of the arbitrarily defined time periods during which their own addiction was of substantial duration. To be eligible for interview, each addict must have had at least two periods of addiction in Baltimore, separated by a period of time when he was not addicted.

In order to keep the interviews at manageable length, each addict was asked about two of the time periods during which he was addicted, regardless of the number of time periods for which he might have provided information. In general, almost all of the interviews were based on the addict's initial period of addiction and the second period of addiction following remission.

In all, 48 interviews were conducted with addict informants (24 blacks and 24 whites). Twenty of the addict informants were chosen from the sample used in an earlier study of a community-wide population of addicts. The remainder were recruited from among nominees suggested in early interviews. Respondents received $15 for a one-session interview lasting one and one-half hours, conducted by trained and experienced interviewers; 80 percent of the respondents were previously known to the staff, or to the principal investigator, who has been engaged in drug

research in this area for more than a decade.

THE ADDICTS

In the early 1950's, the addict population of Baltimore was relatively small, largely black and almost entirely male. The number of narcotic addicts, according to police files, did not exceed a few hundred (Nurco et al. 1975). Between 1951 and 1959, most of the individuals who were entering the drug scene were largely from black inner-city neighborhoods, primarily in west Baltimore, and were raised in working-class families. During the ensuing years the major changes have been in the direction of an increase in the total number as well as an increase in the proportion of whites and of females. By 1970, the addict population had increased more than ten-fold, and the trend toward increasing proportions of whites and of women (particularly among blacks) continued.

In the 1950's and earlier 1960's, the black and white addict populations tended to form rather disparate and non-interacting groups (apart from necessary drug-buying transactions) but with the passage of time and the advent of social changes such as urban renewal and trends toward integration, there has been a slight decline in the separation of black and white addicts. However, over time, there has been a continued tendency for the existence of two separate drug subcultures, black and white, differing in kinds of drugs preferred, methods of supporting habits, location of "hangouts," and visibility of drug use (blacks tending to be more visible).

An analysis of the geographical origins of Baltimore City narcotic addicts has revealed a discernible concentration of narcotic abusers in the inner city. In existence in our first time period (1950-1954), this concentration near the center of the city has increased with time, and has also spread to adjacent areas. In addition, new pockets of concentration have appeared in other areas of the city, which, by the 1970's, were not only isolated from one another but also seemed to differ in ethnic and sex characteristics of addict members, although the majority have been black males.

In the early 1950's, an individual's use of narcotic drugs typically began in the late teens, often coinciding with the end of his schooling. Through the 1950's and early 1960's, there was a gradual decline in the age of starting to use narcotic drugs; this may have occurred originally as a result of greater availability and popularity of pharmaceutical narcotics such as liquid codeine. There is some evidence indicating that starting ages have reverted to those characteristic of the early 1950's, although older addicts have tended to perceive the addicts of the 1970's as very young (possibly an impression resulting from being middle-aged).

In the period of the early 1950's when the addict population was small, addicts of each race tended to be known to one another, i.e., to be "like a small family," characterized by feelings of mutual trust and dependency, as well as willingness to share or

provide help with drugs, skills, and information. In the 1960's, and certainly more recently, these group feelings declined markedly, so that by the late 1960's and early 1970's relations among addicts have deteriorated to a climate described as "cut-throat." Within addict groups of the 1950's and early 1960's, there was often some community of interests extending beyond the shared use of drugs, and embracing recreational activities such as music, as well as in-group customs. With the increase in numbers of young addicts, there was some tendency toward a polarization of younger and older addict populations in association and behavior. In fact there appeared to be two separate cultural orientations. The younger generation of addicts has been described as the "now generation," looking for a quick and easy way to get money for drugs.

When we explored with our addict informants how social changes may have affected the drug scene, their awareness of the world around them seemed to be extremely narrow and restricted; they made virtually no comments about wars, economic changes, political events, urban development, technological and industrial changes, etc. Their detachment was further evidenced by their ignorance and lack of interest in foreign sources of heroin.

Pathways to addiction did not reveal marked changes during the period from 1950 through 1977. Reported first experiences with narcotic drugs have been, for the most part, similar over time. Addicts were first introduced to narcotics by an older friend or acquaintance, a relative of a friend, a family member, or someone encountered in the neighborhood or at a social occasion. Explanations for having started and having continued to use narcotic drugs are also similar throughout our time period. Some of the most frequently cited reasons in our study have included curiosity, peer pressure, escape from boredom, ego support, and pleasure. Perhaps the most significant of these was peer pressure.

THE DRUGS

In the early 1950's, the clearly preferred drug in the Baltimore black addict community was heroin. At that time, heroin was easily obtained, reasonably priced, and considered to be of very good quality by the standards of 1977. Since cutting agents were relatively safe dilutants, there was little likelihood of health hazards such as abscesses resulting from chemical contamination. Because the strength of the drugs was fairly consistent, the chance of overdosing was not great for those addicts of relatively stable tolerance levels. Because of heroin's fairly high strength and low cost, a heroin habit of even long standing could be well supported with little money.

Another popular narcotic drug was liquid codeine, obtainable in the 1950's in the form of over-the-counter (non-prescription) cough remedies known in the addict community as "syrup." Each four-ounce bottle could be used as a narcotic agent and could produce euphoria and addiction. They were often "drunk" by younger teenagers, and were frequently cited as the "path to

addiction" by addicts who started using "syrup" and later went on to heroin. In the 1950's, "syrup" was obtainable with little restriction at all drugstores.

In this period of the early 1950's, the quite small population of white addicts typically preferred "drugstore dope," i.e., pharmaceuticals, to heroin, although white users of heroin did exist. The category of "drugstore dope" included Dilaudid (one of the most favored), morphine, codeine, Dolophine, Demerol, and Pantopon. Some white addicts also used non-narcotic drugs such as amphetamines, barbiturates, and cocaine. Pharmaceuticals were perceived as "safer" narcotics; because they were not cut and the strength and composition of the drugs were known, they provided "safe highs." "Drugstore dope" was obtained primarily from drugstore burglaries, thefts of physicians' medical bags, and often through forging prescriptions or "conning" physicians.

In the later 1950's, the kinds of narcotic drugs available had not changed greatly. Heroin was still the major narcotic used by blacks. Cutting agents were the same as in the early 1950's. Any illness, infections, abscesses, etc. resulting from heroin use in this period tended to stem primarily from using unsterilized "works" (syringe, etc.). Codeine syrups had become very popular and were used extensively. "Syrup" was often used by heroin addicts to avoid or relieve withdrawal symptoms when heroin was unavailable to them. Some also turned to the very inexpensive "syrup" when they needed to use their money for other expenses. "Syrup" also attracted many addicts who wished to avoid the necessity of injecting a drug, and those unwilling to resort to criminal activities to support a heroin habit. The threat of prosecution applied also to heroin purchase and use, while at this time purchase and use of codeine syrups were still entirely legal. Pharmaceuticals were still relatively popular with whites. In "panics" (periods when heroin was scarce), blacks might turn to alcohol or barbiturates. Combinations of drugs were used and indeed preferred by many addicts.

During the 1960's, the purity of heroin gradually declined, with a greater variety of synthetic chemicals being used as cutting agents. By this period, overdosing occurred with some frequency since addicts could not be certain of the drug's strength, or might use too much in an attempt to get a reaction from the weaker substance. Also, many of the chemical contaminants used to dilute heroin caused itches, rashes, and abscesses, the latter in part because addicts injected the weaker drugs more frequently. In this period pharmaceuticals became increasingly difficult to obtain because of intensified security measures instituted by pharmacists and physicians as sophistication about narcotics developed. One of the greatest changes in the 1960's was the removal of codeine syrups from the over-the-counter category. By the later 1960's, liquid codeine had become scarce, and obtainable primarily on the black market at high prices. Another great change occurring in the late 1960's, related to the proliferation of therapeutic programs providing methadone maintenance, was the appearance on the streets of

methadone, first in tablet or powdered form, later as liquid.

The trends of the 1960's continued into the 1970's. Heroin became steadily more costly, and was cut with many chemical substances and household materials. The heroin was considered rather unsafe and "firing" frequently resulted in itching, swellings, infections, and illness. A decline in the quality began in 1971 and continued. Prices varied greatly, according to quantity and quality, but a daily heroin habit in the most recent years of our study required from $50 to $150. Many addicts felt that the heroin had become so diminished in quality that it was not worth the effort involved in trying to obtain it. In the last few years, there has been a gradual return to the use of pharmaceuticals, as addicts forged prescriptions for use in pharmacies in counties around Baltimore City. By the end of our study, methadone was widely used; it was sometimes used in combination with Valium or cocaine.

OBTAINING DRUGS

Before 1950, the addict community of Baltimore City was small and intimate. Addicts and the few dealers who supplied them were well known to one another. There were feelings of mutual trust between buyers and sellers. Dealers were typically found in certain locations; there were in fact only a limited number of "pockets" in Baltimore where narcotics were sold. Traditionally, some of the most popular hangouts for black addicts were located along and surrounding Pennsylvania Avenue. In the early 1950's, dealers carried their stock of narcotics with them, selling "out of their pockets," so that a purchase usually involved a direct and immediate exchange of money and drugs. At this time, most of the dealers working the streets were themselves addicts and their reputations as dealers were usually known to other addicts; also any addict might at some time also sell drugs. In this period, drugstores freely sold "paraphernalia" which could be used for "firing" (injecting) heroin, such as syringes, as well as empty capsules (used as containers for heroin) and commonly used cutting agents. Relations between dealers and addicts tended to be smooth and amicable. At this time there was little contact with the police; although the Narcotic Squad had been organized early in 1951, addicts of that era perceived the police as little threat to them. Investigations, arrests, and convictions were more likely to be responses to the petty larcenies in which the addicts engaged than to any direct violation of narcotics laws. The general public was comparatively naive and uninvolved in matters of drugs.

In the early 1950's, almost all dealers were black. The small minority of white addicts had to locate a black dealer; most typically, they would use a black go-between to buy drugs for them. Occasionally a white addict might gradually develop a relationship of familiarity and trust with a black dealer and might therefore become the buyer for other white addicts, thereby supporting his own habit. White buyers were usually charged higher prices than blacks were, often for drugs of lesser quality. Addicts

using codeine rather than heroin were not involved with dealers. Many white addicts avoided problems of purchasing drugs through the more common white preference for pharmaceuticals, typically obtained through thefts, burglaries, forgeries, and "conning," rather than by commercial transactions.

In the later 1950's and early 1960's, the following changes occurred in the process of obtaining narcotic drugs: activity of the police increased; consequently, dealers stopped "carrying" narcotics, rather "stashing" them nearby. As numbers of addicts increased, buyers had to travel some distance to find dealers; this, as well as increase of public awareness, led to the rise of "shooting galleries"; these gradually decreased in the late 1960's and early 1970's. Areas of selling proliferated and spread; although the original center-city location persisted as a core of drug traffic, areas of drug traffic also spread to the city's periphery and surrounding suburbs. The 1960's also saw the rise of the "profiteer" dealer, who was less likely to be an addict himself; the increase of profiteer dealers paralleled a decrease of trust in dealers. Also the number of dealers and their mobility increased. Baltimore dealers regularly travelled to New York for sizeable quantities of heroin to sell on the streets of Baltimore.

Addicts pursued both legitimate and illicit activities to obtain narcotic drugs. In the early 1950's, it was possible to support a habit by legitimate sources of income, such as employment, funds from parents, pawning possessions, gambling, or funds from welfare. These techniques became increasingly inadequate for supporting a habit in the 1960's and 1970's. Even in the 1950's, however, many black addicts supported their habits by petty crimes, usually non-violent in nature, and white addicts typically obtained pharmaceuticals by illicit means, i.e., theft, burglary, and forgery. As the cost of heroin rose and competition for supplies increased, illicit activities for obtaining funds to support a heroin habit tended to involve more serious crimes of less skill and more violence, the latter often directed to others within the addict community.

Addicts' major perception of available help for problems associated with narcotic addiction focused on methadone maintenance programs which originated in the mid-1960's and proliferated fairly rapidly. Addicts' opinions of the value and contributions of methadone maintenance therapy covered a broad spectrum, ranging from enthusiastic support to bitter opposition. Positive reactions often stressed the advantages of methadone maintenance over heroin addiction in its elimination of the necessity for criminal activities, and for searching for the drug, as well as the fact that tolerance to methadone does not increase as is true of heroin. Major criticisms of methadone maintenance focused on beliefs that methadone created a new addiction, and was also damaging to health, as well as sapping initiative.

Addicts who have sought help from drug abuse treatment programs have been motivated by legal pressures (an alternative to imprisonment), family pressures, or the desire to change their lives. Some addicts are apparently also obtaining methadone simply as a substitute for heroin, or to sell on the streets.

An interesting finding characterizing the outlook of a majority of the addict and ex-addict informants is the almost unanimous opinion that conditions during the early years of addiction were far better than those of later years, irrespective of the specific decade which they described. This we think of as the "good old days" phenomenon, which appears to stem from several conditions: the dramatic quality of the first experience with narcotics; the easier life of the addicts' youthful years; the fact that there is often a period of a few years before the addict is identified by the authorities (a period of relative freedom); the increase in drug tolerance over time, diminishing the impact of the drug; and the fact of the difficulty of the addict's life which causes him to "burn out."

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A Quantitative Method for Determining the Effects of Opiates on Fetal Rats *In Utero*

Kirby, M. L.

INTRODUCTION

Morphine's ability to modify movement in adult animals is well documented (Wikler, 1945; 1950). Its effects include depression of spontaneous activity, depressed simple somatic polysynaptic reflexes and enhanced extensor thrust. With small doses of opiates the monosynaptic reflexes are unchanged; however, with larger doses these too are depressed. McGinty and Ford (1976) treated pregnant rats with opiates and found that the offspring exhibited decreased spontaneous movement and whole-body-startle response to touch.

Fetal rat behavior has been studied in utero by several investigators (Angulo y Gonzales, 1932; Narayanan, Fox and Hamburger, 1971; Raney and Carmichael, 1934; Windle et al, 1935). Fetal rats exhibit two types of activity: spontaneous movement and reflexes. Spontaneous movement begins late on day 15 of gestation (Angulo y Gonzales, 1932) and peaks at day 18 when the fetus is active almost 50% of the observed time (Narayanan, Fox and Hamburger, 1971). Reflexes can be elicited from the vibrissal region and the palmar surface of the forepaw on day 16, and by day 18 all areas of the body are sensitive to stimulation (Narayanan, Fox and Hamburger, 1971).

Because the effects of opiates on fetal movement have not been observed the present investigation was undertaken to determine the feasibility of quantifying the effects of opiates and their antagonists on fetal spontaneous activity and reflexes in utero.

MATERIALS AND METHODS

Pregnant Wistar rats (Charles River) were obtained on the sixth day of gestation. On the 18th day of gestation each dam was anesthetized with ether. An incision was made on the dam's back at approximately the level of the midthorax. The fascia and dorsal musculature were dissected away from the vertebral column and the dorsal arch removed. The exposed spinal cord was transected completely with a pointed scalpel and the incision

closed with suture. The cord transection was at the T6-T9 spinal level (Gelderd and Chopin, 1977). The dam was immobilized on a plexiglas board and a laparotomy was performed just above the inguinal region. The dam's hindquarters and abdomen were immersed in a bath of physiological saline maintained at 37°C, and the uterine horns were allowed to float outside the abdominal cavity submerged in the warm saline. Fifteen to twenty minutes was allowed for the dams to recover from the ether and the fetuses to acclimatize to the saline bath.

Spontaneous activity was observed through the uterine wall with a magnifying lamp or dissecting microscope. At 18 days of gestation the uterine wall is translucent, and even subtle fetal movements can be observed. Spontaneous activity was recorded by the observer by pressing event markers wired into a Grass Model 3 Polygraph. Activity was monitored continuously in a single fetus for periods ranging from 45 to 90 minutes. In one rat, fetal activity was recorded for 45 minutes and observed 3 hours later. Activity did not change during 3 hours of observation. Three uninjected fetuses served as controls. For each of the other fetuses observed, a control record was obtained for 20 minutes before any drugs or saline were injected. After 20 minutes, saline, morphine or naloxone was injected subcutaneously into the dam's pectoral region. After fetal activity was recorded for an additional 20 minutes, saline, morphine or naloxone was injected into the opposite side of the dam and fetal activity was recorded during a third 20-minute period. Morphine and naloxone were injected in various concentrations in physiological saline. Naloxone was injected in appropriate concentrations to reverse visibly the effects of morphine on the dam within 2 minutes after injection. The amount of time each fetus spent in spontaneous movement was calculated as a percentage for each one-minute interval of the record. The percentages derived from each fetus studied were plotted for each minute of the record on standard 1/10 inch grid graph paper. The points were connected to obtain a time-activity curve (fig. 1). The area under a 15-minute interval of the time-activity curve after administration of each drug was determined using a planimeter (fig. 1). A similar period of time under the time-activity curve was measured prior to any drug administration. The areas measured after each injection were calculated as a percentage of the area measured during the control period (fig. 1). A time-activity curve was constructed for each control fetus and each of the curves was subdivided into three 15-minute periods. The area under each period of the curve was measured and areas under the second two periods calculated as a percentage of the first period. These percentages were compared with the percentages derived from saline-naloxone treated fetuses and were found to be not statistically different. The saline treated fetuses were compared with the pooled morphine treated fetuses by a 2-tailed t test and a significant variation was found. Finally, the naloxone periods were compared to the morphine periods in a paired t-test and found to be significantly different.

Figure 1

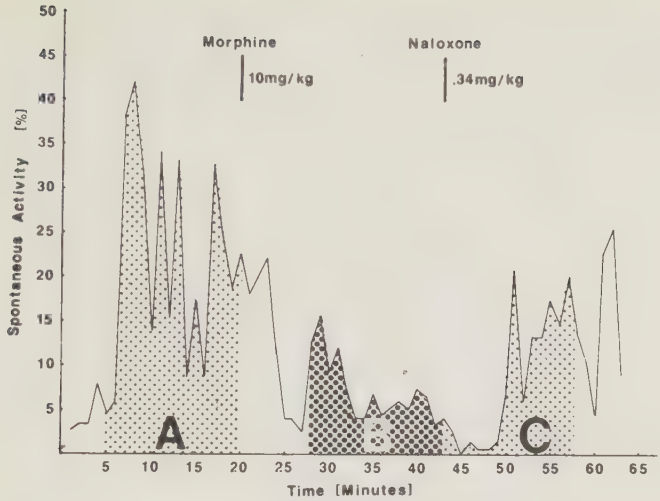

Figure 1. Time-activity curve constructed as described in the text. The curve is divided into three periods as shown by stippled areas. These areas are measured with a planimeter.

Period	Area	% of A
A. 5 to 20 minutes	3.39 in.^{2}	
B. 28 to 43 minutes	1.02 in.^{2}	30
C. 43 to 48 minutes	2.06 in.^{2}	61

Reflexes were studied in additional animals. For these tests the uterine wall was cut at the antimesometrial border and the fetuses allowed to float in saline with the amnion intact. Reflexes were elicited with a sharpened probe or a probe heated in boiling water to 50-60°C (measured with a thermister coupled to an ohmmeter calibrated for the appropriate temperature range). Ten stimuli of each type were applied to the snout, dorsum of paw, or shoulder region at 30-second intervals. Three or 4 fetuses were tested in each dam. Ten mg/kg of morphine was injected into the dam as described above and reflexes retested after 20 minutes. Naloxone was injected in an appropriate concentration to reverse the effects of the morphine on the dam and the fetal reflexes were tested again 5 minutes after injection. The number of positive responses for 10 stimuli was recorded. A one-way analysis of variance was performed to determine significance of the differences in the response level after various drug treatments.

RESULTS

The control fetuses showed bursts of spontaneous activity for 2-to-4 minute intervals followed by short periods of relatively little activity throughout the record. The same pattern was observed after 3 hours. The same type of control record was obtained for all the animals studied which were not chronically injected with morphine. The level of activity was unchanged by the injection of saline or naloxone (table 1). When morphine was injected at concentrations between 0.3 mg/kg and 20 mg/kg there was a depression of activity (table 1). The amount of depression showed a trend of dose-dependence with 0.3 mg/kg causing the least depression and 20 mg/kg causing the most severe depression of activity (table 1). In general this represents a dose-related depression of activity. However, it should be emphasized that the sample for each dose is not large enough to confirm this trend. With the present data it can be stated conclusively that morphine administration causes a depression in fetal spontaneous activity. The injection of naloxone alone caused no significant change in spontaneous activity (table 1). The fetal response to naloxone following morphine injection was not uniform. In 5 out of 8 fetuses

Table 1

Acutely Injected Animals

Animal	Morphine (mg/kg)	Activity*	Naloxone (mg/kg)	Activity*
1.	0(Saline)	106	0.5	117
2.	0(Saline)	125	0.5	114
3.	0(Saline)	114		
4.	0.30	86	0.08	36
5.	1.25	22	0.16	53
6.	1.25	60	0.16	177
7.	5.00	45	0.23	81
8.	5.00	58	0.23	165
9.	10.00	30	0.34	61
10.	10.00	23	0.34	23
11.	20.00	18	0.64	20
	Naloxone (mg/kg	Activity*	Morphine	Activity*
12.	1.00	129	3.5	104

*Expressed as % of control activity

naloxone caused an increase in activity after morphine injection. In 3 of these the activity did not attain control levels (53%, 81%, 61%) while in 2 cases activity was increased over control activities (177% and 165%). A paired t-test revealed a significant increase in activity after naloxone treatment following acute morphine administration.

The average number of reflexes for control periods varied depending on which area was stimulated. Snout was most sensitive to stimulation and responses were consistently 9-10 responses for 10 stimuli (table 2). Paw and shoulder were less sensitive and averaged 5 and 6 responses for 10 stimuli. Paw was eliminated from consideration in the heated probe test because it could not be stimulated discretely. The number of responses decreased significantly for each area after morphine injection and returned to control levels after naloxone injection. Paw and shoulder reflexes tended to be more localized than snout reflexes which occasionally started mass movements in the fetuses.

Table 2

The effects of acute morphine and naloxone injection on reflexes of 18-day fetal rats.

A. Pin Prick

	Snout	Paw*	Shoulder
Control	9.3	5.0	6.0
Morphine (10 mg/kg)	3.5	2.0	2.0
Naloxone (.12 mg/kg	9.8	6.3	7.0

B. Heated Probe (50-60°C)

	Snout	Shoulder
Control	9.6	5.0
Morphine (10 mg/kg)	4.8	1.0
Naloxone (.12 mg/kg)	8.7	5.2

*Table 2. The average number of fetal responses elicited by 10 stimulations with a pin prick (A) and heated probe (B). Testing was done prior to drug treatment (control), 20 minutes after injection of 10 mg/kg morphine subcutaneously in the dam, and 5 minutes after injection of .12 mg/kg of naloxone to reverse the effects of the morphine. The differences in responses are significant at the $p < .01$ level except for column marked * which is significant at $p < .05$ level.*

DISCUSSION

This study demonstrates the feasibility of quantitatively evaluating the effects of morphine on fetal spontaneous activity and reflexes *in utero*. The effects of acute morphine injection on 18-day fetal rats are similar to that of adult animals (Wikler, 1945; 1950). In all cases there is a decrease in spontaneous activity and polysynaptic reflexes after an acute injection of morphine is given to the dam. Naloxone following acute morphine injection reverses the morphine effect on both activity and reflexes.

Placental transfer of opiates has been measured in pregnant rats from day 11 to day 21 of gestation (Blane and Dobbs, 1967; Kirby, 1978; Sanner and Woods, 1965; Yeh and Woods, 1970). Morphine traverses the placenta with increasing facility as gestation progresses (Kirby, 1978). Peak concentrations of morphine are found in the fetus 1 hour after subcutaneous injection of the mother (Kirby, 1978). The changes in fetal activity following morphine injection occurred within 20 minutes. It is possible that the depression of fetal activity would be more remarkable by one hour after injection. However, since the fetuses are metabolically stable in *in utero* studies for an indeterminate amount of time, all the experiments should be carried out as rapidly as possible. Therefore, the effective dose of morphine in fetal studies must be related to a predetermined time period. The latency period of the lowest doses of morphine appeared to be about 13 to 16 minutes. Hence 20 minutes seems a reasonable predetermined time period.

In conclusion, it is possible to quantitatively assess the effects of morphine and naloxone on fetal activity and reflexes and it appears that the effects on 18-day rat fetuses are similar to those seen in adult animals.

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Differential Effects of Opioids on Flurothyl Seizure Thresholds in Rats

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INTRODUCTION

Morphine and related compounds have recently been subdivided into at least three different classes on the basis of diverse subjective effects in man (Jasinski, 1977), different sensitivities towards naloxone (Takemori, 1973), and dissimilar pharmacological profiles both *in vitro* (Lord et al. 1977) and *in vivo* (Martin et al. 1976). We have extended the *in vivo* profile approach to include altered seizure threshold as a measure and have classified twenty opioids by comparing qualitative effects, dose-response curves of enantiomers, sensitivities towards naloxone, and by conducting tolerance and cross-tolerance studies. In light of these experiments, we now report that opioids can be classified into at least four groups *in vivo*. Three of the groups show good correspondence with a classification obtained using the chronic spinal dog preparation (Martin et al. 1976). The fourth group represents a new category; meperidine and pentazocine are the prototype analgesics.

MATERIALS AND METHODS

Animals

The animals used were male Sprague-Dawley albino rats (Zivic-Miller Laboratories) weighing 300-350 g. They were housed in groups of 4-6 per cage at 22 ± 1°C; food and water were available *ad libitum*. A standard light-dark cycle was maintained with a timer-regulated light period from 6 a.m. to 7 p.m.

Flurothyl-Induced Seizures

Groups of 10-20 rats received vehicle or test agent by s.c. injection 30 min before being exposed to flurothyl (Indoklon), a volatile convulsant (Adler, 1975). When appropriate, naloxone was injected s.c. at the same time as the test agent. The flurothyl was given as a 10% solution in 95% ethanol (v/v) to rats placed individually in one-gallon glass jars. The flurothyl was infused onto a gauze pad which was positioned in a perforated metal basket

attached to the underside of the screw cap. A constant rate of infusion of 0.10 mℓ/min was maintained by a Harvard pump. The time interval between the start of the infusion and the onset of a clonic convulsion was considered the seizure threshold. Testing took place between 10 a.m. and 1 p.m. Mean seizure thresholds for rats injected acutely with saline were routinely in the range of 350-380 sec.

Tolerance and Cross-Tolerance Studies

Groups of 12-16 rats were injected s.c. twice daily (at 8 a.m. and 5 p.m.) for 11 consecutive days with vehicle or one of the test compounds listed in table 1. The last injections took place at midnight on day 11. At 9 a.m. on day 12 the rats received the vehicle, the same test compound (tolerance studies), or a second test compound (cross-tolerance studies) s.c. and were exposed to flurothyl 30 min later.

Table 1

Doses of test compounds used in the multiple-injection schedules

Compound	Day/Dose (mg/kg) per Injection		
	Day 1	Day 2	Days 3-11
Cyclazocine	1.25	2.5	5
Levorphanol	2.5	10	20
Meperidine	6.25	6.25	12.5
Pentazocine	6.25	12.5	25

Test Compounds

Most compounds were dissolved in saline and the doses calculated in terms of the particular salt (see acknowledgements). Sparingly soluble benzomorphans were dissolved in a few drops of glacial acetic acid, the pH adjusted to 5 with $NaHCO_3$, and the solution made up to volume with saline. Each compound was injected s.c. in a volume of either 1 or 2 mℓ/kg body weight.

RESULTS

The opioids could be subdivided into the 4 groups shown below.

Group 1

The sigma (σ) receptor agonists (Martin et al. 1976), SK & F 10,047 (N-allylnormetazocine) (10-40 mg/kg) and cyclazocine (1-5 mg/kg) (figure 1A), raised the seizure threshold in a dose-related manner. These psychotomimetic benzomorphans caused behavioral activation and side-to-side head movements in the rats during the period of flurothyl challenge. Both enantiomers of cyclazocine raised the seizure threshold; (-)-cyclazocine was 1.6 times more

potent than (+)-cyclazocine. Naloxone (1 and 10 mg/kg) had no significant influence on the anticonvulsant effects of either cyclazocine or SK & F 10,047. Reverse tolerance developed to the anticonvulsant action of cyclazocine. Specifically, the mean seizure threshold (± s.e.m.) was 330 ± 11 sec in rats pretreated for 11 days with vehicle and subsequently challenged with vehicle; the corresponding values were 447 ± 20 sec and 481 ± 23 sec in rats pretreated with vehicle and cyclazocine, respectively, and subsequently challenged with cyclazocine (5 mg/kg).

Group 2

Several mu (μ) receptor agonists raised the seizure threshold (table 2). The dose-response curve for etorphine is presented in figure 1B. In contrast to our observations with SK & F 10,047 and cyclazocine, behavioral depression was associated with the anticonvulsant effects of the μ receptor agonists. Unlike (+)- and (-)-cyclazocine, only (-)-methadone possessed anticonvulsant properties; (+)-methadone slightly *lowered* the seizure threshold. Interactional studies with naloxone further differentiated the compounds in Groups 1 and 2. Thus, very low doses of naloxone (10-100 μg/kg) could attenuate the anticonvulsant effects of the three μ receptor agonists tested: etorphine, morphine, and (-)-methadone. Importantly, (-)-naloxone (100 μg/kg) antagonised the anticonvulsant effect of etorphine whereas the same dose of (+)-naloxone had no marked effect (figure 2). Finally, tolerance developed to the anticonvulsant effect of levorphanol (20 mg/kg) in rats pretreated for 11 days with levorphanol. Rats from this study were also cross-tolerant to the anticonvulsant effect of morphine (50 mg/kg).

Table 2

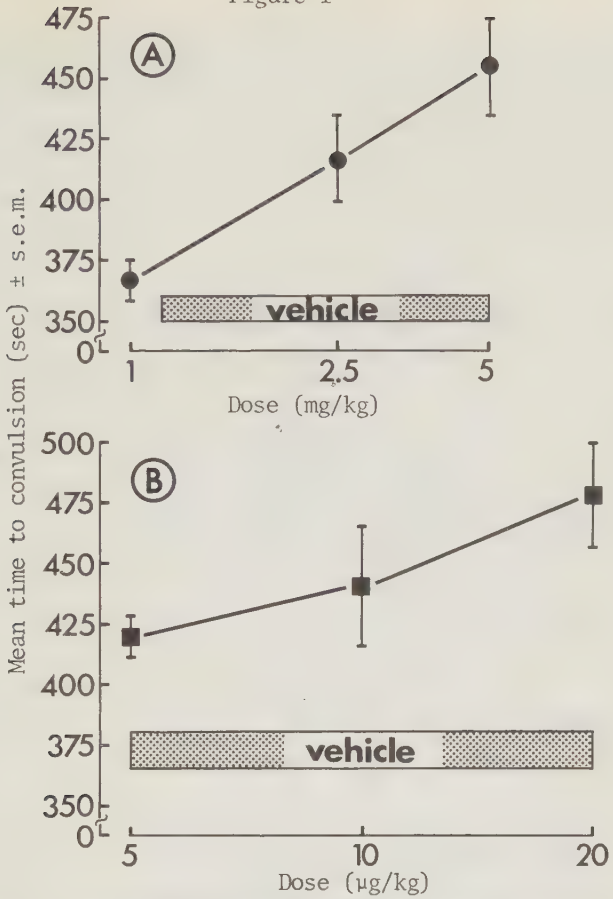
The effects of several μ receptor agonists on seizure threshold (S.T.) in rats challenged with flurothyl

Compound	Dose range (mg/kg, s.c.)	Max. % change in S.T. relative to controls
Etorphine	0.005-0.02	+28.6
Morphine	12.5-64	+25.6
(-)-Methadone	1.25-5	+22.8
Phenazocine	0.5-5	+18.0
Levorphanol	2.5-20	+17.5
Buprenorphine	0.004-12.5	+15.2

Group 3

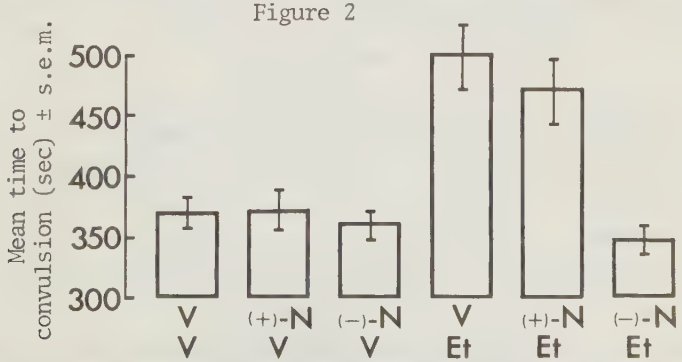
The following compounds had no clear (or dose-related) effects on seizure threshold: cyclorphan (1-80 mg/kg); ethylketocyclazocine (0.5-50 mg/kg); ketazocine (0.5-20 mg/kg); moxazocine (12.5-50 mg/kg); nalbuphine (5-20 mg/kg); nalorphine (25-100 mg/kg); naloxone (0.01-10 mg/kg); norcyclazocine (6.25-25 mg/kg) and normorphine (50-100 mg/kg).

Figure 1



Dose response curves for (A) cyclazocine and (B) etorphine in the rat flurothyl test.

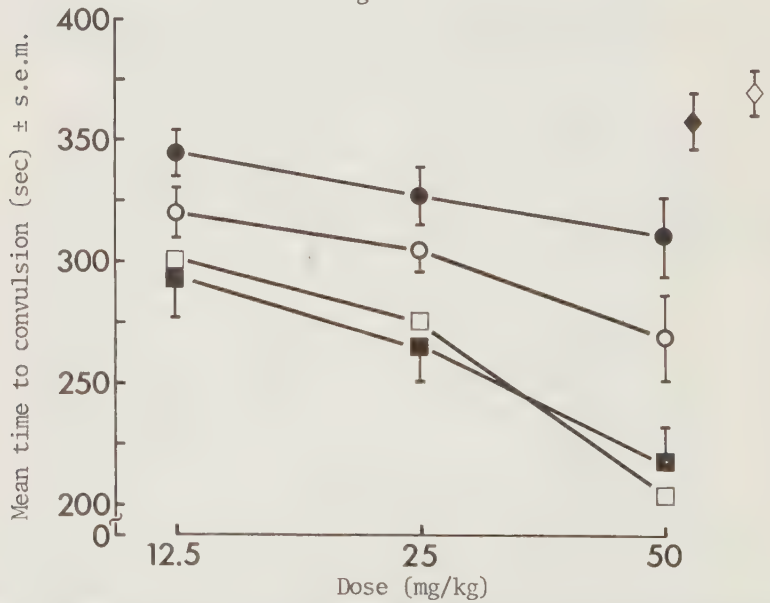
Figure 2



Stereospecific antagonism of the anticonvulsant effect of etorphine (Et, 20 µg/kg) by (-)-naloxone (N, 100 µg/kg). V = vehicle.

Dose-related proconvulsant effects were obtained with meperidine (12.5-50 mg/kg), pentazocine (12.5-50 mg/kg), and normeperidine (1.56-50 mg/kg). The maximum percent changes in seizure threshold (relative to controls) were 19.2%, 31.5%, and 46.8%, respectively. Both enantiomers of pentazocine lowered the seizure threshold; (+)-pentazocine was 5.6 times more potent than (-)-pentazocine. The proconvulsant effects of meperidine and (-)-pentazocine were potentiated by naloxone. At 10 mg/kg (but not at 1 mg/kg) naloxone displaced, in a parallel, downward direction, the dose-response lines of both analgesics. Naloxone (10 mg/kg) had no marked influence on the already substantial proconvulsant effects of (+)-pentazocine (figure 3). Although the naloxone-normeperidine interaction gave a trend towards potentiation, no statistically significant differences were obtained. Tolerance did not develop to the proconvulsant action of meperidine. There was no cross-tolerance between meperidine and etorphine. In other words, etorphine (0.02 mg/kg) still had a marked anticonvulsant action in rats that had received multiple injections of meperidine. Reverse-tolerance developed to the proconvulsant action of pentazocine. Specifically, the mean seizure threshold (± s.e.m.) was 359 ± 11 sec in rats pretreated with vehicle and subsequently challenged with vehicle; the corresponding values were 281 ± 9 sec and 232 ± 22 sec in rats pretreated with vehicle and pentazocine, respectively, and subsequently challenged with pentazocine (30 mg/kg).

Figure 3



Dose-response curves for (+)-pentazocine (■) and (-)-pentazocine (●) in the absence (closed symbols) and presence (open symbols) of naloxone (10 mg/kg). Vehicle control (◆); naloxone (10 mg/kg) (◇).

DISCUSSION

In the present study, twenty opioids have been separated into four groups using the conventional *in vivo* approaches of dose-response relationships, stereospecificity, naloxone-sensitivity, and tolerance/cross-tolerance. It seems that analgesics classified as μ receptor agonists in the chronic spinal dog preparation (Martin et al. 1976) are likely to raise seizure threshold in our model. The receptor mediating this effect has the classical features of stereospecificity, sensitivity towards (-)-naloxone, and susceptibility to tolerance. A second receptor mediates the anticonvulsant actions of SK & F 10,047 and cyclazocine, two σ receptor agonists that cause bizarre behavioral effects in rats. This receptor is only weakly stereospecific, the *levo*-rotatory enantiomer of cyclazocine being the preferred ligand. Naloxone insensitivity and resistance to tolerance are further features of this receptor.

Several compounds have no pronounced effect on the flurothyl-induced seizure threshold. Present in this group are four analgesics (ethylketocyclazocine, ketazocine, nalbuphine, nalorphine) that possess only low physical dependence capacities in withdrawn, morphine-dependent monkeys. It remains to be seen if this classification is fortuitous or is indeed an additional characteristic of certain κ receptor agonists.

Our finding that meperidine and pentazocine are not grouped with the prototype μ, κ, and σ agonists is in keeping with the difficulties experienced by others in trying to define the position of these analgesics relative to other opioids (e.g. Martin et al. 1978). We are unable to state, unequivocally, that the proconvulsant actions of meperidine and pentazocine are mediated by a subclass of opioid receptors as opposed to being merely a reflection of non-specific, stimulant effects. There seems to be a naloxone-sensitive link in the mechanism of action of (-)-pentazocine and meperidine since the proconvulsant effects of these analgesics were *enhanced*. The fact that such enhancement was not obtained with compounds possessing minimal narcotic analgesic activity (normeperidine, (+)-pentazocine) may indicate that further subdivision within Group 4 is possible. In this regard, Gilbert and Martin (1975) view meperidine and normeperidine as having different modes of action in producing convulsions in mice.

In conclusion, our data support current theories of multiple opiate receptor types. Furthermore, the model may well be suited for detecting novel narcotic antagonists since the receptors involved mediate effects that are (a) antagonized, (b) enhanced, or (c) unaffected by naloxone, the standard narcotic antagonist. Antagonists with profiles different from naloxone have been a recurring need; their availability will most likely prove critical in the discrimination of opiate receptors just as the advent of specific antagonists was associated with major advances in the areas of, say, adrenergic and histaminergic pharmacology.

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Intravenous Phencyclidine Self-Administration by Rhesus Monkeys Leading to Physical Dependence

Balster, R. L.; Woolverton, W. L.

Phencyclidine (PCP) has been shown to reinforce i.v. drug self-administration behavior in rhesus monkeys (Pickens et al., 1973; Balster et al., 1973). Self-administration studies can by used as an animal model to study both the reinforcing properties of PCP and the consequences of self-administered doses of PCP. Previous research (e.g. Deneau et al., 1969; Yanagita and Takahashi, 1970; Winger and Woods, 1973; Johanson et al., 1976) has shown that unlimited access i.v. self-administration can result in high levels of drug intake with characteristic toxicities for various classes of abused drugs. In the cases of opioids, barbiturates and ethanol, amounts sufficient to produce physical dependence are self-administered. This paper summarizes the results of i.v. PCP self-administration in rhesus monkeys given continuous access for an extended period of time. Very high PCP intakes were observed which led to the development of physical dependence.

METHODS

The subjects were five adult male rhesus monkeys. Each monkey was housed in an individual self-administration cubicle and fitted with a stainless steel tubular harness (Deneau et al., 1969) and connecting arm. Under anesthesia the animals were prepared with venous catheters. The catheter exited through the skin on the back and connected through the harness and arm to a peristaltic infusion pump.

Self-administration sessions were conducted beginning at noon each day. At the beginning of the session two white lights were illuminated over each lever and each left lever press response resulted in a 10 sec infusion of the drug or vehicle solution. During infusions the left lever lights changed from white to red. Responses on the right lever produced the same stimulus changes over the right lever but no infusion resulted. At 11:00 a.m. the subsequent morning the session was terminated, the data recorded, the equipment checked, the cages cleaned, and the food intake over the preceding 23-hour period determined.

The experimental design was as follows. For the first 7 sessions, left lever responses resulted in saline injections. For the next 30 sessions, responses resulted in 0.01 mg/kg injections of PCP. Following access to 0.01 mg/kg PCP, the unit dose of PCP was increased to 0.05 mg/kg/inj. for 20 sessions, after which time saline was again made available. In most cases the subjects were returned to PCP and a second withdrawal period was studied.

In addition to food intake other observations were made of the subjects' general behavior. During withdrawal, a symptom checklist was used to score withdrawal signs every 4 hours until recovery. Plasma PCP concentrations were determined by Dr. B.R. Martin using a GC/MS method substantially the same as that described by Lin et al. (1975).

RESULTS

TABLE 1 summarizes the results of unlimited access to PCP in all animals. The data are divided into the periods of access to saline and 10-day segments of access to PCP at both the low and high dose.

Table 1

INTRAVENOUS PHENCYCLIDINE SELF-ADMINISTRATION IN RHESUS MONKEYS

Daily Injections, Drug Intake, Incorrect Responding and Food Intake in Different Phases of the Study

Monkey	Injections/Session Mean	Injections/Session Range	Mg/Kg/Day Mean	Incorrect Rs/Session Mean	Incorrect Rs/Session Range	Food Intake (g) Mean	Food Intake (g) Range
			Sessions 1-7 1.0 ML/INJ Saline				
3147	23	1-103	-	22	4-37	200	200-200
M155	111	65-199	-	44	14-108	142	65-200
M193	4	0-17	-	17	0-55	180	170-200
M258	4	1-9	-	9	0-31	190	170-200
M266	37	13-63	-	25	5-64	192	170-200
			Sessions 8-17 0.01 MG/KG/INJ PCP				
3147	211	9-514	2.1	37	7-123	135	30-200
M155	283	47-473	2.8	64	13-157	119	50-180
M193	77	0-336	0.8	14	0-48	135	0-180
M258	36	3-181	0.4	26	0-71	200	200-200
M266	406	167-693	4.1	212	31-548	113	15-200
			Sessions 18-27 0.01 MG/KG/INJ PCP				
3147	578	8-851	5.8	86	11-247	99	200-195
M155	484	288-734	4.8	86	20-224	58	20-130
M193	21	3-137	0.2	7	2-19	174	125-200
M258	88	1-305	0.9	19	0-70	195	145-200
M266	554	4-1003	5.5	260	1-678	95	0-200

Table 1 (continued)

Monkey	Injections/ Session Mean	Range	Mg/Kg/ Day Mean	Incorrect Rs/ Session Mean	Range	Food Intake (g) Mean	Range
		Sessions 28-37 0.01 MG/KG/INJ PCP					
3147	744	138-1211	7.4	20	1-57	176	60-200
M155	513	67-827	5.1	101	1-390	124	0-200
M193	113	25-315	1.1	13	5-47	129	0-200
M258	89	0-214	0.9	7	0-25	123	20-185
M266	400	8-807	4.0	67	0-155	80	0-200
		Sessions 38-47 0.05 MG/KG/INJ PCP					
3147	238	62-331	11.9	28	0-96	137	55-180
M155	222	116-282	11.1	42	6-138	118	25-185
M193	151	7-206	7.6	44	0-110	49	0-200
M258	164	86-237	8.2	91	9-255	136	30-200
M266	258	171-298	12.9	34	1-95	75	50-130
		Sessions 48-57 0.05 MG/KG/INJ PCP					
3147	294	207-340	14.7	27	3-118	148	125-195
M155	163	130-202	8.1	42	8-125	164	120-185
M193	180	93-276	9.0	63	0-167	43	0-190
M258[a]	233	61-398	11.7	64	2-183	163	55-200
M266	131	71-168	6.6	149	6-365	125	80-175
		Readdiction 0.05 MG/KG/INJ PCP					
3147[b]	288	183-372	14.4	10	0-46	141	70-180
M258[b]	163	175-286	12.1	83	25-343	130	50-135
M266[c]	284	190-387	14.2	52	3-149	115	30-190

[a]Sessions 48-59 [b]Sessions 63-75 [c]Sessions 61-72

During the first seven sessions of access to saline, few injections were administered, usually averaging less than 50 injections per session. The exception was M155 who had prior experience with drug self-administration. Incorrect lever responding was about as frequent as correct lever responding, again with the exception of M155. Food intake usually exceeded 170 grams during this period. During the initial 10 day access to PCP (0.01 mg/kg) average drug intake ranged from 0.8-4.1 mg/kg/day. Three of 5 animals (3147, M155, M266) readily initiated responding for this dose of PCP and achieved substantial levels of intake. Self-administration was more erratic in the other two monkeys. Incorrect lever responding also increased somewhat, though not as much as responding on the correct lever. Food intake was markedly decreased, particularly during sessions in which PCP intake was highest. Over the next 20 sessions of access to this dose of PCP, intake gradually increased

in all animals, with one animal achieving an average daily intake of 7.4 mg/kg between sessions 28 and 37. In spite of increasing PCP intake, food intake returned toward baseline levels, evidence for tolerance to this effect of PCP. During this period, the animals that reliably self-administered PCP maintained virtually continuous intoxication. They were able to sit but only by supporting themselves with their arms. Legs were often splayed in an uncharacteristic manner and vertical nystagmus and tongue movements were prominent.

When the dose per injection of PCP was increased to 0.05 mg/kg PCP, all animals self-administered the drug readily with less daily variability in intake than at the low dose. For the animals that had reliably responded for 0.01 mg/kg PCP (3147, M155, M266), injections/session decreased but not in proportion to the change in dose. Consequently, overall intake increased, frequently resulting in total daily intakes greater than 10 mg/kg. For animals that were less reliable in their self-administration of 0.01 mg/kg PCP (M193, M258), the 5-fold increase in unit dose resulted in an increase in the average number of injections per day and roughly a 10-fold increase in mean total intake. Incorrect lever responding did not change in a systematic manner with the changes in unit dose. Concurrent with the increased drug intakes at the higher dose, food intake once again decreased and failed to return to baseline levels during this period. When animals again had access to PCP after the first withdrawal period (the readdiction phase) all animals promptly resumed responding at or above previous levels.

At the higher unit dose, all monkeys maintained an even more pronounced intoxication than at the lower dose. Typically they would be found lying in awkward positions on the cage floor in the vicinity of the response lever, unable to support themselves. In one case (M193), lying in awkward positions and inability to move apparently reduced blood flow to various parts of the body resulting in gangrenous extremities. This animal died before withdrawal data could be obtained.

On session 58 (and again after the readdiction phase) saline was substituted for PCP and the behavior of the animals scored on an observational rating scale every 4 hours. A summary of the observations is presented in TABLE 2.

Table 2

INCIDENCE OF PCP WITHDRAWAL SYMPTOMS

	Monkey			
Symptom	3147	M155	M258	M266
Vocalizations	X	X	X	X
Fearfulness	X	X	X	X
Bruxism	X	X	X	X
Oculomotor Hyperactivity	X	X	X	X
Diarrhea	X	X	X	X

TABLE 2 (continued)

INCIDENCE OF PCP WITHDRAWAL SYMPTOMS

Symptom	Monkey 3147	M155	M258	M266
Refuse Preferred Food	X	X	X	X
Piloerection	X	X	X	-
Tremors	X	X	-	X
"Nodding Off"	-	X	X	X
Ear and Facial Twitches	X	-	X	X
Priapism	X	-	-	X
Abdominal Contractions	-	-	-	X
Emesis	-	-	-	X
Convulsions	X	-	-	-
Most Intense Episode	Severe	Moderate	Mild	Severe

Although the spectrum of symptoms varied somewhat between animals, generally the following observations were made. By 4 hours the animals had substantially recovered from PCP intoxication, were eating and less ataxic. At 8-12 hours, animals became markedly hyperresponsive with a distinctive conjugate oculomotor hyperactivity that was not the same as nystagmus characteristic of the intoxication. The animals usually refused preferred foods. At its maximum (12-16 hours) several of the following abstinence symptoms were present: piloerection, tremor, diarrhea, continuous vocalizations, hyperresponsitivity, oculomotor hyperactivity, priapism, bruxism and ear and facial twitches. Abdominal contractions and emesis were observed in one animal, while convulsive activity could be elicited in another. Characteristically, food intake was reduced by about 50% during withdrawal. Over the next 24 hours the symptoms gradually diminished. The entire spectrum could be immediately reversed by the i.v. administration of PCP (0.25 mg/kg). I.V. naloxone (0.1 mg/kg) failed to precipitate withdrawal.

Blood samples were taken at various times during the readdiction phase and during the second withdrawal period in two monkeys (M258 and M266) for determination of plasma levels of PCP. These levels ranged from 105 to 280 ng/ml, and decreased to 0-12 ng/ml within 24 hours of saline substitution.

DISCUSSION

The conclusions of this experiment may be summarized as follows:

(1) Rhesus monkeys will respond for intravenous PCP delivery at doses of 0.01 and 0.05 mg/kg. The reinforcing properties of PCP have been shown previously (Pickens et al., 1973; Balster et al., 1973). This study confirms and extends those previous reports.

(2) The rate and pattern of responding with continuous access to PCP is in part related to the unit dose. At the lower dose (0.01 mg/kg) generally higher response rates could be obtained than with

the higher dose (0.05 mg/kg), however response rates were more variable, both from session to session and within-sessions. Although response rates were lower at the higher unit dose they were not proportionately lower, thus daily drug intake increased with unit dose.

(3) Unlimited access to PCP self-administration results in dose levels producing marked intoxication. Since drug intake was higher during access to the higher unit dose, the intoxication was more pronounced during this phase. In most cases this constant severe intoxication led to effects on food intake, sleep and body positioning which resulted in a deterioration of the health of the animals.

(4) Food intake was always suppressed by PCP. For some monkeys, tolerance to this effect was evident.

(5) Unlimited access to PCP self-administration at 0.05 mg/kg/inj. leads to intakes producing plasma levels of PCP in the range of 100-300 ng/ml.

(6) Unlimited access to PCP self-administration can result in continuous intakes of PCP sufficient to produce physical dependence as evidenced by a withdrawal syndrome. This is perhaps the most novel observation in this experiment and requires some comment. PCP has not previously been reported to produce physical dependence, although studies designed to evaluate this phenomenon have not been carried out. On the other hand, McCarthy and Harrigan (1976), also using unlimited access self-administration as well as continuous intravenous infusion in rhesus monkeys, found evidence that ketamine produced physical dependence. The symptoms observed were very similar to what we observed with PCP. They included piloerection, tremors, irritability, preconvulsive activity and a single episode of clonic convulsions.

Seven instances of PCP withdrawal were observed in this study. The most consistent finding was the time course for this syndrome following abrupt discontinuation of i.v. self-administration. The onset was between 4-8 hours, with a peak from 12 to 16 hours and recovery by 24-48 hours. The severity and specific symptom complex differed somewhat from subject to subject, although separate episodes in the same animal were generally quite similar. Neuromuscular symptoms were prominent in all animals. Bruxism and vocalizations were common and in some cases very striking. Gastro-intestinal symptoms included diarrhea in most cases, apparent abdominal pain, and emesis in one case. All the animals refused highly preferred foods during withdrawal and normal food intake was often disrupted. Other signs and symptoms occassionally seen included piloerection, priapism and in one monkey on two occasions convulsions. Some of the animals appeared exhausted during withdrawal, frequently closing their eyes and apparently falling asleep even while being watched by an observer (what we termed "nodding off").

On three occasions we were not able to precipitate the syndrome with i.v. naloxone. On the other hand, it was possible to completely reverse the symptoms of withdrawal immediately with i.v. PCP. In

short, PCP appears capable of producing physical dependence in the rhesus monkey. This dependence is not of the morphine-type, but may be common to other arylcycloalkylamines (e.g. ketamine).

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Effects of Chronic Treatment With Morphine, Methadone, and LAAM on the Response to Phencyclidine in Rats

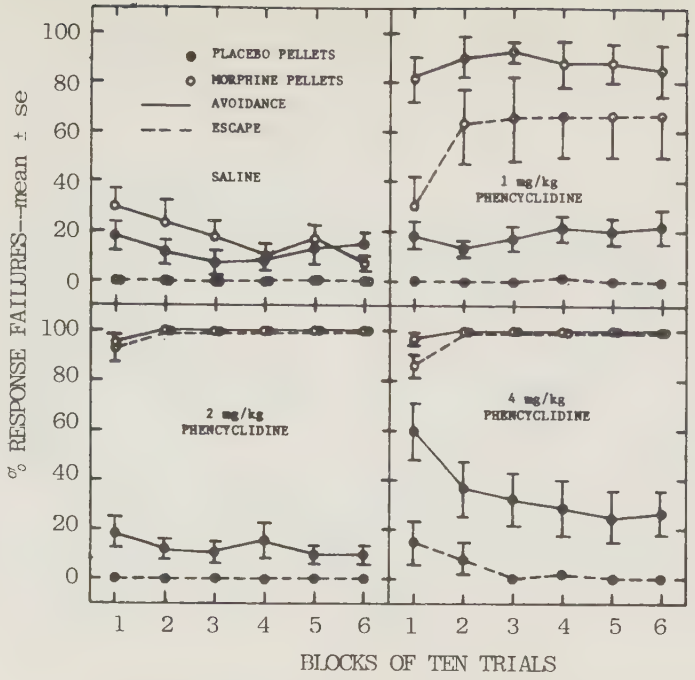
Pryor, G. T.; Howd, R. A.

Many people regularly taking narcotics that they obtain on the street or during maintenance therapy are known to use other drugs for recreational or therapeutic reasons (Du Pont 1976). The possibility that chronic narcotic use may alter the response to or disposition of other drugs has received only limited attention. Recently we have been engaged in a survey of the effects of chronic treatment with morphine, methadone, and LAAM on the response to and disposition of a number of commonly used or abused drugs. We found that in addition to pentobarbital the response to thiopental, phenobarbital, and barbital were all enhanced and prolonged after chronic treatment with morphine by pellet implantation (Howd and Pryor 1979). Moreover, we found that the response to diazepam and ethanol were similarly enhanced and prolonged, all of which suggest that chronic treatment with morphine significantly affects systems other than the hepatic drug metabolizing enzymes. We recently examined phencyclidine, because of the increase in street abuse of this drug (Petersen and Stillman 1978) and the fact that it is often misrepresented as a number of other drugs such as LSD, mescaline, and Δ^9-tetrahydrocannabinol.

METHODS

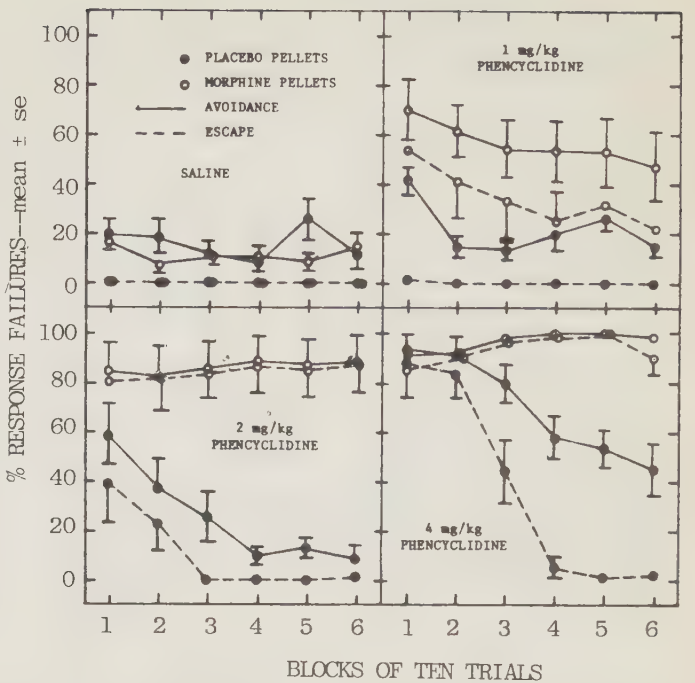
Male Fischer strain rats were used. The apparatus and procedures for establishing a multisensory conditioned pole-climb avoidance/escape response (CAR) have been described (Pryor et al. 1977). Briefly, the rats were taught to escape a 1.0 mA foot shock by climbing or pulling an aluminum pole suspended from the ceiling of the test chamber. This response terminated the trial. Then they were taught to avoid the foot shock by responding in the presence of a pulsating change (2.5 per minute) in the intensity of the house light or a 4 kHz tone or a nonaversive current (120 μA) on the floor. Each stimulus was presented separately on a given trial and preceded the aversive foot shock by 10 seconds. If the rat failed to respond (avoidance failure), the stimulus and the aversive foot shock remained on for 20 seconds. An escape failure was recorded if the rat did not respond throughout the trial.

FIGURE 1



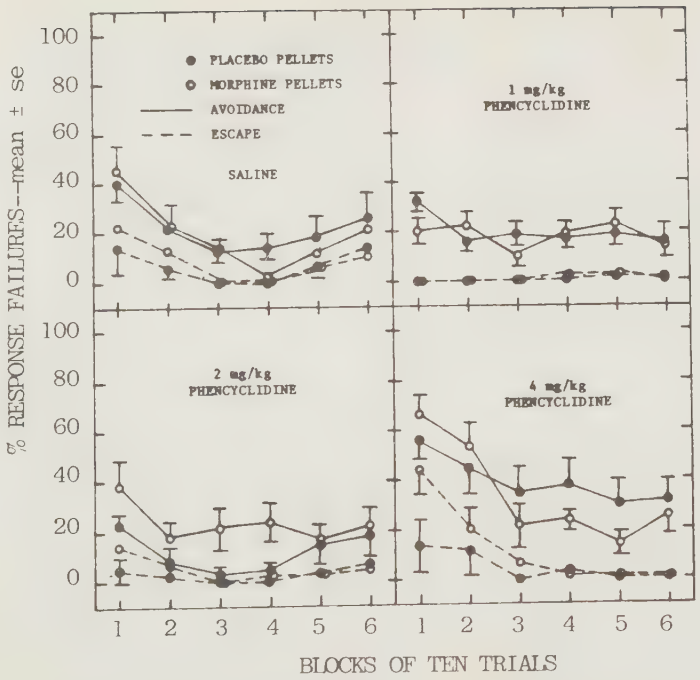
Placebo- or morphine-pelleted rats were tested after ip injection of saline or phencyclidine on Day 8 (N = 9 per group, total N = 72).

FIGURE 2



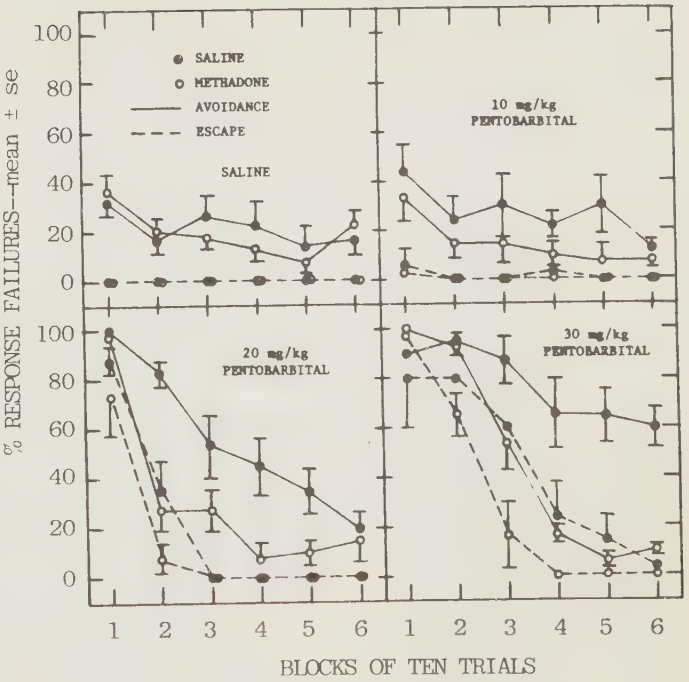
Placebo or morphine-pelleted rats were tested again after ip injection of saline or phencyclidine on Day 16.

FIGURE 3



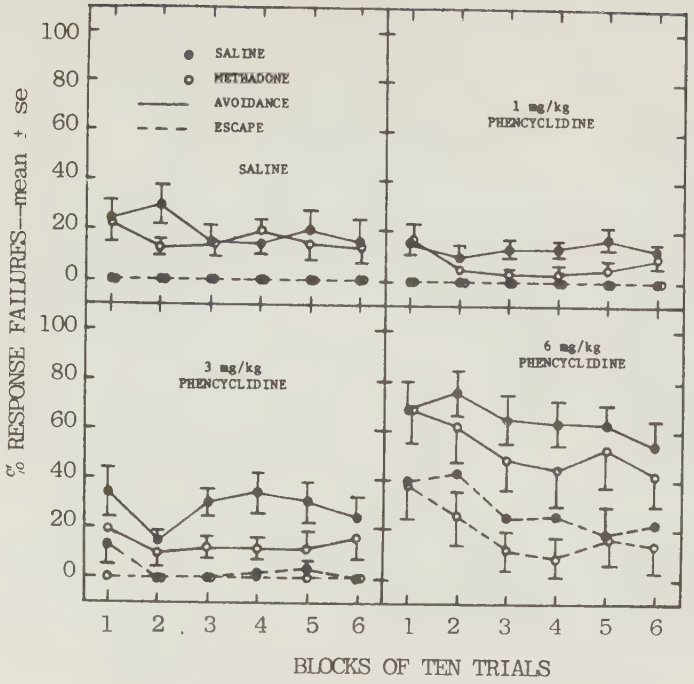
Placebo- or morphine-pelleted rats were tested again after ip injection of saline or phencyclidine on Day 32.

FIGURE 4



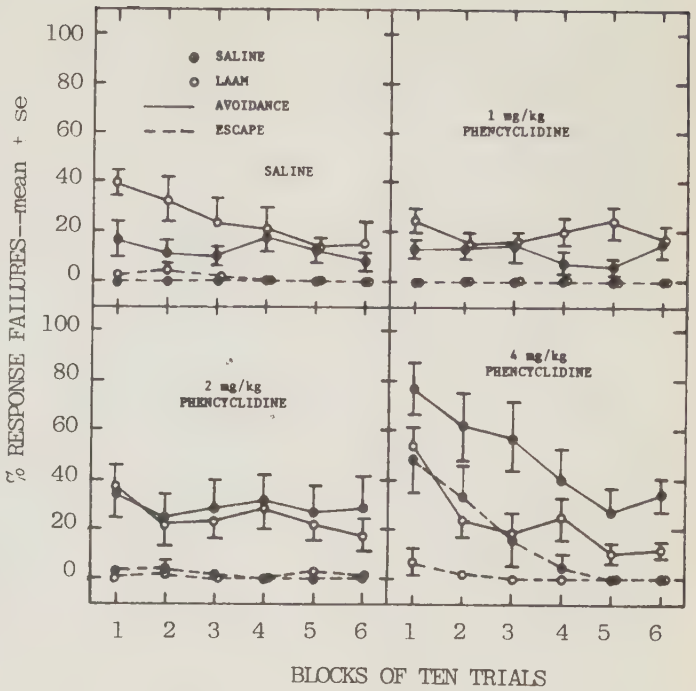
Rats treated daily with saline or methadone were tested after ip injection of saline or pentobarbital on Day 16 (N = 9 per group, total N = 72).

FIGURE 5



Rats treated daily with saline or methadone were tested again after ip injection of saline or phencyclidine on Day 44.

FIGURE 6



Rats treated daily with saline or LAAM were tested after ip injection of saline or phencyclidine on Day 24 (N = 9 per group, total N = 72).

For morphine the pellet-implantation technique was used (Gibson and Tingstad 1970). One placebo or morphine (75-mg base) pellet was implanted subcutaneously on the nape of the neck under light ether anesthesia. Two additional pellets were implanted 3 days later. The pellets were not removed. For methadone and LAAM the drugs were dissolved in 2 ml/kg saline and given daily by oral intubation. The initial dose of 5 mg/kg of methadone was increased by 2.5 mg/kg on days 6, 11, 18, 25, 36, 47, and 59. The initial dose of 1 mg/kg of LAAM was increased by 1 mg/kg on days 6, 8, 10, 14, 18, and 22. For each test the rats were given nine warm-up trials to reinstate the avoidance response. Then they were injected ip with saline or 1 of 3 doses of phencyclidine HCl (Phillips Roxane, Inc., St. Joseph, Missouri; 2 ml/kg) and given a 60-trial test.

RESULTS

Figure 1 shows that when tested on the 8th day, 1 and 2 mg/kg phencyclidine had no significant effects on the CAR performance of placebo-pelleted rats and 4 mg/kg had only minimal and short-lasting effects, whereas both avoidance and escape responses were severely impaired by all doses of phencyclidine in morphine-pelleted rats throughout the 60-trial test session. The impairing effects of phencyclidine on CAR performance 12 days after the last placebo or morphine pellets were implanted were still clearly enhanced and prolonged in the morphine-pelleted rats compared with placebo-pelleted controls (Figure 2). However, this effect was not as great as it was the week before, indicating some recovery from the chronic treatment with morphine. The effects of chronic treatment with morphine on the response to phencyclidine had dissipated completely when the rats were tested 28 days after the last pellets were implanted (Figure 3).

As shown in Figure 4, chronic treatment with methadone decreased the duration of the impairing effect of pentobarbital on CAR performance when tested on the 16th day. Similar results were obtained when the test with pentobarbital was repeated on the 30th day. The effects of phencyclidine were tested on the 44th day. Chronic treatment with methadone did not, like chronic treatment with morphine, increase the potency or duration of action of phencyclidine (Figure 5). The trend at all doses was toward less effect of phencyclidine after chronic treatment with methadone than with saline.

The effects of phencyclidine were tested after 24 days of treatment with LAAM. Figure 6 shows that LAAM, like methadone, did not increase the potency or duration of action of phencyclidine. Also, like methadone, there was less effect of the 4 mg/kg dose of phencyclidine after chronic treatment with LAAM than saline. We tested the rats with pentobarbital on the 51st day of the experiment. Chronic treatment with LAAM, like methadone, clearly and markedly shortened the duration of action of this barbiturate (data not shown).

DISCUSSION

Our results show that chronic treatment with morphine markedly enhanced and prolonged the impairing effects of phencyclidine in our test system. Phencyclidine is metabolized in rats primarily by ring oxidation (Munch 1974; Wong and Biemann 1976). Therefore, because chronic treatment with morphine decreases the activities of other ring oxidative enzymes (Kato and Onoda 1966; Clouet and Ratner 1964; Masten, Price, and Burnett 1978), it probably also decreases phencyclidine metabolism to some extent. However, the magnitude of the enhanced phencyclidine response was surprisingly large and other mechanisms may be involved.

In contrast to chronic treatment with morphine, the effects of phencyclidine were not enhanced after chronic treatment with methadone or LAAM. Instead, there was some evidence for the opposite response. Indeed, the duration of the effects of pentobarbital was shortened appreciably by chronic treatment with both methadone and LAAM. This latter effect was probably related to the induction of hepatic microsomal enzymes reported by others (Masten et al. 1974; Masten, Price, and Burnett 1978) for these narcotics. In view of the clear effect on the response to pentobarbital, it was somewhat surprising that a similar effect on the response to phencyclidine was not observed.

Chronic treatment with morphine appears to enhance and prolong the pharmacological effects of a variety of psychoactive drugs. Along with our present results with phencyclidine, the list of such drugs now includes amphetamine, several of the barbiturates (hexobarbital, pentobarbital, phenobarbital, thiopental, and barbital), the minor tranquilizers meprobamate and diazepam, and ethanol. Although chronic treatment with morphine has been shown to decrease the metabolism of some of these drugs, this mechanism alone cannot account for all the interactive effects observed (e.g., barbital). Other dispositional effects such as changes in absorption, distribution, and elimination may be involved to a greater or lesser extent. However, it is also possible that chronic treatment with narcotic agonists causes neurochemical or neurophysiological changes in the brain such that the pharmacological response to these drugs is enhanced. Failure to see such an enhanced response after methadone and LAAM may have been due to the metabolic cross tolerance caused by these narcotics that masked the cerebral changes or prevented their development.

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Dependence Within the Opiate-Sensitive Neurone

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Abstract

The basic principle is proposed that the neurone possessing specific opiate receptors (opiate-sensitive neurone) is the primary and sufficient site of opiate dependence and associated tolerance (ODT). The lines of experimental evidence that support this principle are: (a) in the dependent rat, drugs, such as atropine, that block transmission between neurones lessen some signs of withdrawal, intensify others and leave yet others unchanged, whereas opiates suppress and specific opiate antagonists intensify all withdrawal signs; (b) in the mouse and in the post-ganglionic myenteric plexus of the guinea-pig ileum, as dependence intensifies, so the effective concentration of naloxone falls below that at which naloxone interacts only with the opiate receptor; (c) ODT can be demonstrated in single neurones in situ in the rat cerebral cortex and the myenteric plexus of the guinea-pig ileum; (d) ODT can be induced in the guinea-pig isolated ileum by exposure to opiate in conditions of transmitter blockade, both of ganglia and of the neuromuscular junction; (e) ODT develops in cultured opiate-sensitive neuroblastoma x glioma cells, which are functionally separate. The principle that the opiate-sensitive neurone is the primary and sufficient site of ODT eliminates about half of the hypotheses that have been advanced to explain the mechanism of ODT and points towards a small group of hypotheses that postulate intracellular mechanisms.

Introduction

Several hypotheses of the mechanism of opiate dependence and associated tolerance (ODT) imply that this condition occurs within the neurone that responds directly to opiates through specific opiate

receptors (opiate-sensitive neurone). Such hypotheses include those involving (a) changes in the opiate receptor (Axelrod, 1956; Collier, 1966; Snyder, 1975), (b) hypertrophy of the cyclic AMP mechanism inhibited by interaction between opiate and receptor (Collier and Roy, 1974; Sharma, Klee and Nirenberg, 1975; Traber, Gullis and Hamprecht, 1975), and (c) damming up of unreleased transmitter (Crossland and Slater, 1968; Paton, 1969). Long after these hypotheses were first proposed, the evidence has accumulated to the point of conviction that ODT does indeed occur within the opiate-sensitive neurone. This evidence will be discussed under four heads: (a) paradoxical effects of transmitter blockade; (b) increased responsiveness to naloxone; (c) ODT in individual neurones in situ; and (d) ODT in neuroblastoma x glioma cells.

Paradoxical Effects of Transmitter Blockade

Attempts to determine whether any endogenous substances that convey messages between neurones were intimately involved in the mechanism of dependence have provided one of the first pieces of evidence that dependence occurs within the opiate-sensitive neurone, although this interpretation was overlooked at the time the experiments were done.

In 1972, we showed that, in the morphine-dependent rat, heroin, given shortly before naloxone challenge, lessened all the ten signs of precipitated abstinence then being recorded (Collier, Francis and Schneider, 1972). In contrast, substances, such as atropine, indomethacin and para-chlorophenylalanine, which block the action or formation of putative messengers between neurones, inhibited some signs of abstinence, intensified others and left still other signs unaffected. For example, when atropine was given 30 min before withdrawal was precipitated with naloxone, it significantly decreased the incidence of jumping, diarrhea and chewing, but significantly increased that of irritability to touch and of paw tremor, and it did not change the incidence of squeak on handling, teeth chattering, ptosis, head shakes and body shakes. Essentially similar results were obtained when the withdrawal syndrome was modified with an inhibitor of the synthesis of serotonin or of prostaglandins.

That all withdrawal signs are suppressed by opiates and precipitated by opiate antagonists, whereas inhibitors of transmission between neurones have paradoxical effects on the expression of abstinence, argues that the site of dependence in the whole animal is the opiate-sensitive neurone.

Increased Responsiveness to Naloxone

Whole animals. In opiate-naive mice, naloxone does not normally elicit the jumping response, characteristic of withdrawal behavior; but, as exposure to opiate continues and dependence deepens, this response is elicited by increasingly smaller doses of naloxone (Cheney and Goldstein, 1971; Way, Loh and Shen, 1969). Thus, the dose needed to elicit jumping in a highly dependent animal is less than 1/70 of that required at an early stage in the induction of dependence. Because low doses of naloxone probably act

only at the opiate receptor this suggests, although it does not prove, that dependence occurs in the neurones possessing such receptors. For stronger evidence, we must turn to the post-ganglionic part of the myenteric plexus of the guinea-pig ileum.

Post-ganglionic myenteric plexus of ileum. More or less prolonged incubation of the guinea-pig isolated ileum in Krebs solution containing opiate, at 4°C, 20°C or 37°C produces ODT, in the form of a contractant response to a low concentration of naloxone, coupled with a reduced inhibition by morphine of the response to neurally evoked stimulation (Paton, 1957; Hammond, Schneider and Collier, 1976; Villarreal, Martinez and Castro, 1977; North and Karras, 1978; Villarreal and Castro, 1979; Collier, Cuthbert and Francis, 1979). This is a specific effect, since responsiveness to naloxone is not induced by another inhibitory substance -- adrenaline -- and withdrawal is not precipitated by (+)naloxone. This condition in the myenteric plexus resembles in essential characteristics the ODT that has for long been studied in whole animals. Thus, its induction is specific, since it is blocked by (-)- but not by (+)- naloxone (Collier, Cuthbert and Francis, 1979). It is also stereospecific, since it is brought about by (-)-morphine, but not by (+)-morphine (Collier, Cuthbert and Francis, 1979), and by levorphanol, but not by dextrorphan (Hammond, Schneider and Collier, 1976; North and Karras, 1978). Moreover, the degree of ODT produced by incubating the ileum with opiate is related to the concentration of opiate and to the duration of exposure to it (Collier, Cuthbert and Francis, 1979; Hammond, Schneider and Collier, 1976). Furthermore, induction of tolerance in the ileum, as in the whole animal, is blocked by the protein synthesis inhibitor, cycloheximide. That this induction occurs in the presence of hexamethonium (Hammond, Schneider and Collier, 1976), and that hyoscine blocks the contracture elicited by naloxone challenge of the dependent ileum (Collier, Cuthbert and Francis, 1979) indicate that tolerance and dependence here occur in the post-ganglionic part of the myenteric plexus.

In ilea made in this way highly dependent on normorphine, we find that a withdrawal contracture can be elicited by as little as 30nM naloxone (Collier, Cuthbert and Francis, 1979), a concentration that acts only by blocking the opiate receptors of the plexus. Hence, these observations on the ileum lead to the conclusion that the opiate-sensitive neurone is the site of this heightened responsiveness to naloxone and of the dependence that it characterizes. The parallelism between ODT in the myenteric plexus and that in the whole animal argues that the same conclusion applies in vivo.

Individual Neurones in situ

Rat cerebral cortex. Continuous exposure to morphine for 30 min of individual neurones of the rat cerebral cortex in situ induces tolerance and a state of excitation (Satoh, Zieglgänsberger, and Herz, 1976). Likewise, induction of ODT by continued treatment of the whole animal with morphine results in a lessened response to opiate and a heightened response to stimulant substances and to

naloxone of the individual cortical neurone prepared for electrical recording of its nerve impulse production (Satoh, Zieglgänsberger, and Herz, 1976).

Myenteric plexus of guinea-pig ileum. Nerve impulse production by single neurones of the myenteric plexus, made tolerant and dependent by 24 h exposure to morphine, normorphine or levorphanol at room temperature in vitro has been recorded by North and Karras (1978). Such neurones were less responsive to normorphine, but when treated with naloxone, fired impulses at high frequency. Neither hexamethonium nor hyoscine prevented the induction of this state of morphine tolerance and dependence in vitro. These observations demonstrate directly that ODT occurs in the post-ganglionic neurones of the myenteric plexus.

Neuroblastoma x Glioma Hybrid Cells

Neuroblastoma x glioma hybrid cells (strain NG108-15), cultured in the presence of an opiate, develop a form of tolerance and dependence expressed as an increased capacity to produce cyclic AMP (Sharma, Klee and Nirenberg, 1975, 1977; Traber, Gullis and Hamprecht, 1975). Although these cells possess opiate receptors, and the affinity of opiates for these receptors is correlated with their ability to inhibit adenylate cyclase (Sharma, Nirenberg and Klee, 1975); the extent to which induction of tolerance and dependence in NG 108-15 cells resembles that in normal neurones is uncertain, for three reasons. First, it has not been possible directly to connect increases in cyclic AMP level in normal, opiate-inhibited neurones with increased impulse production or transmitter release (Takagi and Takayanagi, 1972; Hayashi, Mori, Yamada and Kunitomo, 1978; Karras and North, 1979; Duggan and Griersmith, 1979). Second, the NG 108-15 cells are not arranged in a stable inter-communicating system, as are neurones of the CNS or myenteric plexus. Third, the NG 108-15 cells are of malignant origin and, unlike neurones, reproduce themselves. There is good evidence, however, that they still develop ODT when their reproduction is inhibited (W.A. Klee, personal communication). Despite these objections, there is no doubt that, after exposure of the culture to opiate, tolerance and dependence occurs within cells that possess specific opiate receptors.

Discussion and Conclusion

Each of the lines of evidence that I have discussed points to the conclusion that ODT occurs within the opiate-sensitive neurone. Since this is the only neurone known to be sensitive to low concentrations of naloxone, the nanomolar sensitivity to naloxone that accompanies the development of dependence in the post-ganglionic part of the myenteric plexus of the guinea-pig ileum leads to the proposition that the opiate-sensitive neurone is the main and sufficient site of ODT.

Table 1

Proposed mechanisms of tolerance (T) and/or dependence (D) compatible with its occurrence within the opiate-sensitive neurone.

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1. Enzyme expansion or contraction (Goldstein and Goldstein, 1968; Shuster, 1961); e.g. increased enzyme destroying enkephalins (Malfroy, et al., 1978) (T/D).

2. Supersensitivity to excitatory or subsensitivity to inhibitory transmitter (Grumbach, 1961; Collier, 1966, 1968; Jaffe and Sharpless, 1968) (T/D).

3. Damming up of transmitter release (Crossland and Slater, 1968; Paton, 1969) (T/D).

4. Change in number (density) or efficiency (affinity and intrinsic activity) of receptors for opiate (Axelrod, 1956; Collier, 1966) (T), or for endogenous messengers (Collier, 1966; 1972) (T/D).

5. Hypertrophy of cyclic AMP system (Collier and Roy, 1974; Sharma, Klee and Nirenberg, 1975, 1977; Traber, Gullis and Hamprecht, 1975) (T/D).

6. Development of cellular immunity to opiates (Cochin and Kornetsky, 1968) (T).

7. Dual receptors: (a) Agonist and antagonist (Snyder, S.H., 1975) (T/D); (b) Excitatory and inhibitory agonist (Jacquet, 1978; Jacquet, et al., 1977) (D).

This proposition does not exclude the possibility that, in nervous systems, other changes, such as supersensitivity to transmitter in a neurone downstream of the opiate-sensitive neurone may also contribute to ODT. Indeed, there is now some experimental evidence for this (Llorens, et al., 1978).

This principle affects both the theory and practice of investigating the opiate dependence mechanism. It appears to be incompatible with six of the thirteen or so hypotheses that have been put forward in recent decades to explain the mechanism of ODT. Among the remaining seven hypotheses (Table 1), this principle particularly favours those that involve changes in the responsiveness of the neurone, such as those of super- and subsensitivity (No. 2) and hypertrophy of the cyclic AMP system (No.5).

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Clonidine Detoxification: A Fourteen-Day Protocol for Rapid Opiate Withdrawal

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INTRODUCTION

Last year at this meeting, in Baltimore, we reported that a single dose of 5 ug/kg of clonidine but not placebo caused a rapid and significant decrease in opiate withdrawal signs and symptoms in patients addicted to methadone (2). More recently, we confirmed these findings for other synthetic opiates and heroin (3). These initial studies suggested a new use for clonidine, an imidazoline drug widely used in the treatment of hypertension (4). We suggested after an open outpatient study, that a nonopiate treatment like clonidine, which could control symptoms during the acute phase of opiate withdrawal and allow the patient to have symptomatic refief while detoxifying, could enable patients to switch to other treatment modalities, especially maintenance on the long-acting opiate antagonist naltrexone. In allowing patients who wish to be opiate free to make it to zero mg of methadone, clonidine detoxification appeared to be superior to the usual treatment of opiate withdrawal (2). During clonidine detoxification the patients experience a few mild opiate withdrawal symptoms which may allow a large number of patients to discontinue their methadone. While our previous studies (2,3,4) offered considerable promise they were complicated by the failure of patients to follow the outpatient protocol for clonidine administration and refrain from use of other drugs after their hospital discharge.

Studies in rodents and primates have suggested that the neurotransmitter, norepinephrine, is involved in opiate withdrawal (4,5,7,8, 11). Our early experience with the alpha-2 adrenergic agonist clonidine (2,3) which reduces brain noradrenergic activity, provided pharmacological support in man for a noradrenergic hyperactivity mediation of opiate withdrawal. We now have given clonidine acutely in a dose of 6 ug/kg and chronically in a dose of 17 ug/kg/day in an inpatient setting to thirty opiate addicts after withdrawal from 10-60 mg or chronic methadone treatment.

SUBJECTS AND METHODS

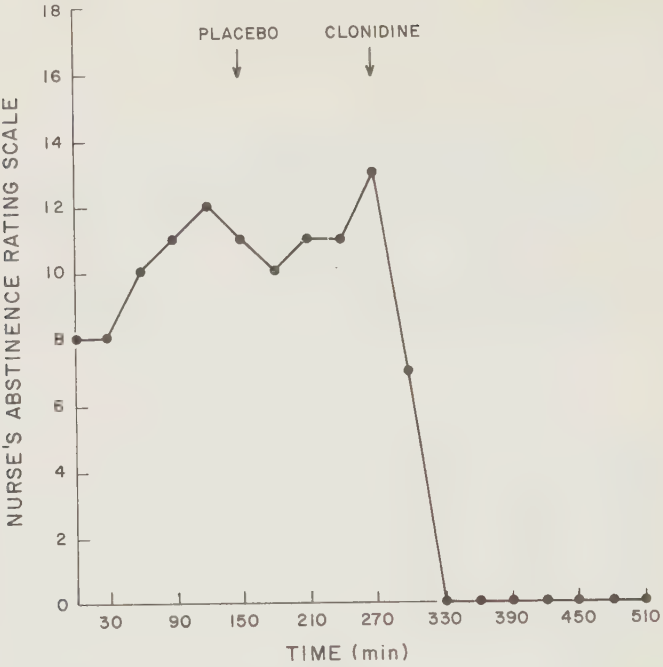
Subjects were members in good standing of methadone maintenance treatment programs for at least six months prior to admission. These thirty patients had been addicted to opiates for up to fifteen years. Average methadone dose was 40 mg/day. Twenty-five of the patients were employed. They all expressed interest in discontinuing methadone and gave informed consent to a study which required an abrupt withdrawal from methadone three days after admission to the Evaluation and Research Unit and at least 36 hours with no opiate administration. All patients had previous unsuccessful attempts at detoxifying from opiates. All had objective signs of opiate withdrawal. Patients were observed for the presence or absence of withdrawal signs and symptoms by a research nurse clinician every hour from 8:00 a.m. while the patients were at bed rest during the day of clonidine administration (4). The nurse rated twenty-one items associated with withdrawal (4) as present (1) or absent (0); the total score being added to give a measure of withdrawal severity. The symptoms and signs were opiate craving, anxiety, yawning, perspiration, lacrimation, rhinorrhea, yen sleep, mydriasis, goose flesh, tremors, hot and cold flashes, aching bones and muscles, anorexia, increased blood pressure, insomnia, increased temperature, increased respiratory rate and depth, increased pulse rate, restlessness, nausea and vomiting, diarrhea and spontaneous orgasm. All patients completed self-rating Addiction Research Center Inventory (ARCI) WOW scales (4) every hour from 9:00 a.m. to assess for self-rated opiate withdrawal symptomatology. After the first day of clonidine administration, the patients were administered clonidine 17 ug/kg/day in divided doses and rated three times a day before clonidine administration for opiate withdrawal symptoms by a research nurse clinician. In addition, all patients completed self-rating analog scales. These analog rating scales were utilized to assess for changes in nervousness, being high, unpleasantness, energy, irritability, fear and anger. They were completed every hour from 9:00 a.m. during the first day of clonidine administration and thereafter completed three times a day prior to clonidine administration. On the first day, the patients took 6 ug/kg of clonidine or placebo orally in matching vehicles to demonstrate the effect of clonidine on opiate withdrawal signs and symptoms and to assess the changes in blood pressure produced by this dose of clonidine. After the initial clonidine and placebo administration, patients without precipitous blood pressure declines were given clonidine 17 ug/kg/day for at least nine days. Clonidine dose was gradually decreased to zero by day fourteen. All patients were excluded who had a previous history of cardiac arrhythmias, hypotension, vasomotor instability, psychiatric illness or hospitalization (6).

RESULTS

Acute First Dose Study

The number of opiate withdrawal signs increased during the baseline period to a peak of 14.0 $\pm$ 0.5 S.E.M. Clonidine 6 ug/kg produced a rapid and significant decrease in opiate withdrawal signs and symptoms to 5.7 $\pm$ 0.8 at 90 minutes and 0.6 $\pm$ 0.2 at 120 minutes and 0.6 $\pm$ 0.2 at 120 minutes (paired t Test $p < .01$). An example of this

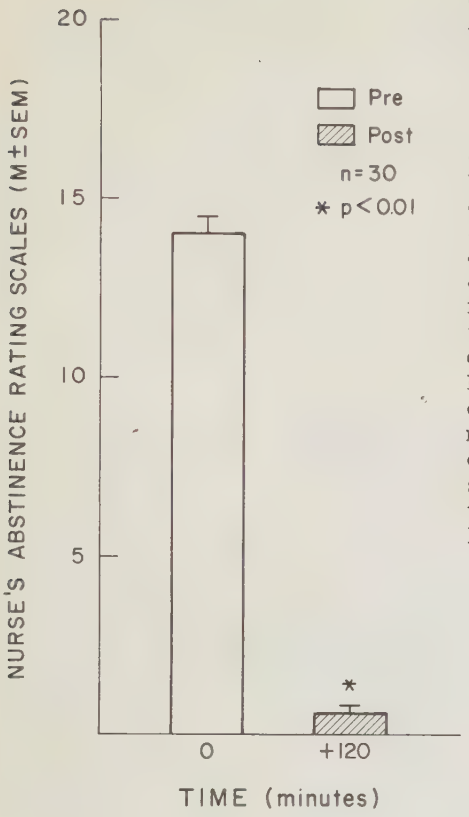
acute effect is shown in Figure 1.



Opiate withdrawal ratings remained unchanged for an additional 240 minutes. Systolic blood pressure was significantly reduced ($p<0.01$) from a pretreatment mean of 130.9 ± 3.2 to 102.4 ± 4.4; as was diastolic blood pressure from a pretreatment mean of 91.4 + 2.2 to 69.7 ± 2.9 at 120 minutes after clonidine administration ($p<0.01$). Blood pressure was not significantly changed over the next 240 minutes. In two patients, systolic blood pressure was reduced to $\leq$60 mm hg at 180 minutes after the first dose of clonidine. This decrease persisted for an additional 120 minutes. ARCI ratings were also significantly ($p<0.01$) reduced from a pretreatment mean of 12.5 ± 1.3 to 6.4 ± 0.5 at 120 minutes after clonidine administration. Relief of subjective and objective distress was significant (see Figure 2).

On self-rating analog scales where 70 is the highest score, there were significant ($p<0.01$) decreases in self-rated nervousness from 54.5 ± 1.4 before clonidine to 31.3 ± 0.8 at 120 minutes and irritability from 48.3 ± 2.6 to 24.6 ± 1.7 at 120 minutes.

Figure 2

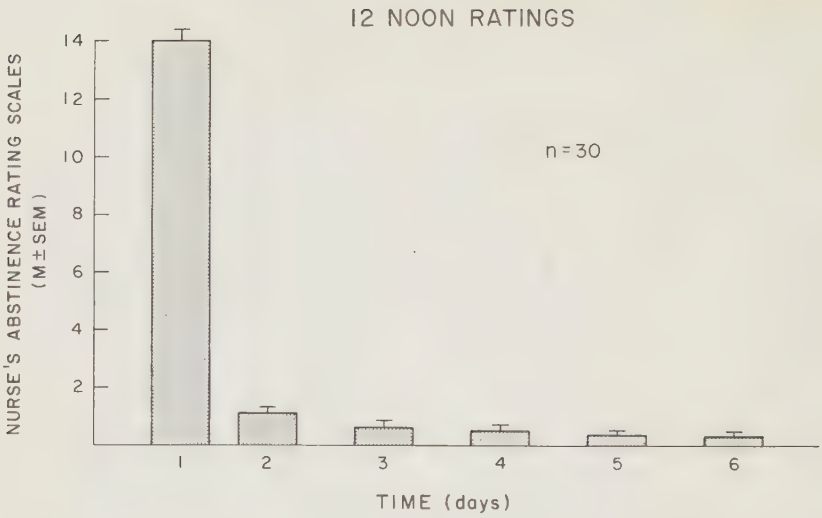


There were no significant changes noted in self-rating analog scales for energy or feeling "high". There was a significant ($p<0.01$) decrease in scores reported for the "uninvolved" and "angry" scales. All patients stated that they needed their methadone and that they were "kicking" immediately prior to clonidine administration. At 120 minutes after clonidine administration, none of the patients stated that they felt the need for methadone or like they were "kicking". Placebo had no significant effects on any of the above measurements or ratings. The effect of clonidine was not significantly different for those patients addicted to 15 or 50 mg of methadone.

Ten Day Study

All 30 patients were continued on clonidine in an inpatient hospital setting. None of the patients chose a return to methadone after their first dose of clonidine. On the first day of clonidine administration, the patients were given 6 ug/kg as a test dose and then 6 ug/kg at bedtime. For the next 9 days patients were given 17 ug/kg of clonidine in divided doses of 7 ug/kg at 8:00 a.m. and 3 ug/kg at 4:00 p.m. and 7 ug/kg at 11:00 p.m. Each day vital signs and nurses' abstinence ratings and self-ratings were done as described previously (4). Clonidine doses were held in some cases due to severe hypotension. There were no significant changes in the abstinence ratings during this ten-day inpatient trial. Twenty-one patients, however, complained of difficulty in falling asleep. Dry mouth, sluggishness, depression and occasional bone pain were more infrequent complaints. Mean twelve noon opiate withdrawal symptoms and signs were 1.1 ± 0.3 on day two, 0.6 ± 0.2 on day three, 0.5 ± 0.2 on day four, 0.3 ± 0.1 on day five and 0.3 ± 0.1 on day six.

Figure 3



Systolic and diastolic blood pressure remained significantly decreased throughout the nine days of 17 ug/kg of clonidine administration. There were no significant increases or decreases in self-rated nervousness, irritability, uninvolved, angry, fear, "high" or energy. On fourteen occasions clonidine dose was decreased to compensate for oversedation or hypotension. On days 11,12 and 13 the clonidine dose was decreased by 50%. On day 14, the patients received no clonidine whatsoever. None of the patients showed any increase in opiate withdrawal signs or symptoms or had the emergence of clonidine withdrawal symptoms using this protocol. On day 14 all patients were given Naloxone (1.2 mg) intravenously to assess for residual opiates or dependence. All Naloxone tests were negative. All of the 30 patients completed the 14-day inpatient study.

DISCUSSION

As compared to our previous studies (2,3,4) the data reported here were not confounded by difficulties in compliance and other drug use. All patients in this study were successfully detoxified from chronic methadone addiction and all were fourteen or more days without any opiate administration at the time of discharge from the hospital. This detoxification success rate is much greater than our experience with methadone detoxification groups. In addition, significant and potentially serious decreases in systolic and diastolic blood pressure were successfully managed in the hospital without the patient incurring additional opiate withdrawal symptoms by frequent vital signs and bed rest.

In this inpatient detoxification study, we have shown that clonidine is a safe and effective non-opiate treatment for opiate withdrawal which suppresses the symptoms and signs of opiate withdrawal as well

as the affective changes associated with opiate withdrawal. Affects associated with withdrawal such as anxiety, irritability and anger were rapidly reduced after clonidine administration. Clonidine is therefore extremely useful as a treatment for detoxification. This 14-day inpatient clonidine detoxification protocol could be useful in the treatment of selected opiate addicts. For example, clonidine detoxification could be linked to maintenance on long-acting opiate antagonists such as Naltrexone. As we demonstrated in the last group of ten patients - clonidine, being a nonopiate, allows the patient to abruptly discontinue opiate administration and be opiate-free long enough to initiate maintenance treatment with Naltrexone. Clonidine detoxification may allow the detoxification of patients maintained on methadone who have had previous unsuccessful attempts to detoxify due to the morbidity of current slow detoxification practices. Clonidine is also potentially useful in the treatment of iatrogenic addictions and the protracted abstinence syndrome where the risk of exposure to opiates might be reduced.

We tested the efficacy of clonidine in opiate withdrawal as a result of studies of the major noradrenergic nucleus, the locus coeruleus (LC), in monkeys. The effects of electrical or pharmacological activation of this nucleus were demonstrated to produce changes which resembled those seen in opiate withdrawal (5-8). Morphine and clonidine blocked the effects of the electrical and pharmacological activation of the LC in primates (5-7). This suggested that opiate withdrawal may be due, in part, to increased noradrenergic neural activity in areas such as the LC which are regulated by both opiates through opiate receptors and clonidine through alpha-2 adrenergic receptors (2). This hypothesis is also supported by the similarity of clonidine and opiate withdrawal with respect to vital signs and mood and the noradrenergic hyperactivity reported in clonidine withdrawal (11). These and other data (1,7-10) have suggested that opiate interactions with noradrenergic areas such as the LC, regulated by both alpha-2 adrenergic and opiate receptors, may become activated in opiate withdrawal-related panic states and possibly naturally-occurring panic states.

In summary, the effects of clonidine on opiate withdrawal in man (2-4) and rodent (1) provide pharmacological support for a noradrenergic hyperactivity hypothesis for opiate withdrawal (2,7,8) and suggest that clonidine reverses opiate withdrawal by replacing opiate-mediated inhibition with alpha-2 adrenergic inhibition of brain noradrenergic activity. Additional basic and clinical tests of this noradrenergic hyperactivity hypothesis are necessary. However, our studies and the studies of Washton and Resnick reported in this monograph suggest that clonidine detoxification is a safe and rapid procedure which may add additional treatment options to the current and standard treatment of the opiate addict. Our data suggest that clonidine detoxification allows 100% of the addicts to become opiate-free and clonidine-free within fourteen days but that maintenance with Naltrexone and group therapy may be necessary to maintain this state.

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Clonidine Hydrochloride: A Nonopiate Treatment for Opiate Withdrawal

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Interest in clonidine hydrochloride as a treatment for opiate withdrawal has been stimulated by the recent findings of Gold, Redmond and Kleber (1978). These investigators found that a single oral dose of .005 mg/kg clonidine produced a rapid and significant decrease in acute withdrawal symptoms, subjective distress, and blood pressure in 11 hospitalized addicts following abrupt discontinuation of 5-50 mg chronic methadone. It was suggested that a new use for clonidine, a nonopiate imidazoline drug widely used in the treatment of hypertension, might be to reduce the morbidity of current opiate detoxification procedures.

Various symptoms that emerge during opiate withdrawal discourage attempts to detoxify and contribute to the large number of patients who are unable to achieve abstinence. A nonopiate medication which could suppress withdrawal symptoms might improve the prognosis for achieving abstinence and allow more patients the option of other treatment modalities, such as the long-acting opiate antagonist, naltrexone (Resnick et al. 1974). The applicability of naltrexone treatment has been limited by the fact that before receiving the first dose of naltrexone patients must detoxify and then remain opiate free for at least several days to avoid a precipitated withdrawal reaction. A potentially important role for clonidine would be to bridge the gap between opiate dependence and naltrexone treatment by providing symtomatic relief during detoxification and the subsequent opiate-free period when relapse rates are extremely high.

Critical questions about clonidine's efficacy as a treatment for opiate withdrawal concern its suitability for use in an outpatient clinical setting. During the past year, at the Division of Drug Abuse Research and Treatment of New York Medical College, the present authors conducted a series of preliminary clinical trials which included upwards of 70 outpatients who attempted detoxification from opiates with the aid of clonidine. In preparation for a carefully controlled investigation, these open clinical trials sought to replicate the single-dose findings of Gold et al. and obtain preliminary information concerning clonidine's efficacy in facilitating outpatient

detoxification from opiates, its side effects and acceptability to patients, and to determine a daily dosage regimen that would maximize clonidine's therapeutic benefit.

I. SINGLE-DOSE TRIALS

Subjects and Methods

A single oral dose of .005 mg/kg clonidine was administered to 12 opiate-dependent individuals experiencing acute withdrawal discomfort from heroin and/or methadone. All subjects were free of serious medical and psychiatric illness and signed an informed consent after the nature of the experimental procedures had been fully explained. Blood pressure measurements and subjective ratings of withdrawal symptoms were taken immediately before clonidine ingestion and again at 2 hours postclonidine. Each of 17 withdrawal symptoms were rated by the subjects on a 4-point scale as either absent (0), mild (1), moderate (2), or severe (3).

Results

The withdrawal rating scores were totalled to give a composite measure of withdrawal severity both pre and postclonidine for each subject, as shown below in Table 1.

Table 1

WITHDRAWAL RATING SCORE TOTALS[1] BEFORE AND AFTER .005 mg/kg CLONIDINE

Subject #	Preclonidine	2 Hours Postclonidine
1	40	9
2	12	2
3	29	9
4	25	6
5	23	5
6	13	0
7	38	6
8	24	11
9	38	16
10	31	2
11	25	4
12	45	15
Mean	22.75	6.25*

[1]The highest possible withdrawal rating score total is 51.
*Mean pre and postclonidine scores differ significantly:
$t = 9.8648$, $df=11$, $p<.001$.

These data show that clonidine produced a marked and significant reduction in withdrawal ratings from a mean of 22.75 preclonidine to 6.25 at 2 hours postclonidine. All subjects reported dramatic relief of their withdrawal discomfort. The symptoms reduced most by clonidine were chills, lacrimation, rhinorrhea, nervousness, stomach cramps and muscle/joint pains. Clonidine side effects consisted of dry mouth, drowsiness, and a decrease of 10-15 mmHg in

systolic and diastolic blood pressure. These findings closely resemble the results of Gold et al. and provide further evidence of clonidine's ability to suppress ongoing withdrawal symptoms.

II. CLINICAL TRIALS

Two methods of clonidine detoxification were employed: one involved a gradual reduction in methadone with simultaneous administration of clonidine and the other involved an abrupt switch from methadone and/or heroin to clonidine.

1. Gradual Detoxification Procedure

Subjects and Methods

The subjects were 20 methadone maintenance patients who requested detoxification to an opiate-free state. After a thorough explanation of the experimental procedures, all subjects signed an informed consent for clonidine and naltrexone treatments. The detoxification procedure involved induction onto clonidine followed by gradual decrements in methadone at a rate of 5 or 10 mg per week with continued daily administration of clonidine. Clonidine was started at .005 mg/kg per day in divided doses and then increased by 0.1 mg steps as needed to a maximum of .010 mg/kg per day. The rate of clonidine dosage increments was tailored for each patient so as to maximize therapeutic benefit and minimize the occurrence of adverse side effects such as sedation and orthostatic hypotension. The maximum daily dose of clonidine ranged from 0.2 to 0.9 mg, with a mean of 0.8 mg/day. At the point where clonidine was introduced, level of methadone dependence ranged from 5-40 mg with a mean of 17 mg. Time on clonidine plus methadone ranged from 2-6 weeks. Upon reaching a zero methadone dose, placebo methadone was introduced. Subjects who reached a zero methadone dose and remained opiate free for 10 days were given an intravenous injection of 1.2 mg naloxone to confirm opiate-free status in preparation for immediate induction onto naltrexone. After the first dose of naltrexone, clonidine was discontinued at varying rates. At each clinic visit the subjects were seen for withdrawal ratings (as described earlier) blood pressure measurements, and adjustment of medication.

2. Rapid Detoxification Procedure

Subjects and Methods

The subjects were 50 opiate-dependent individuals who requested detoxification and gave their written consent to treatment with clonidine and naltrexone after a thorough explanation of the experimental procedures. Twenty-two of the 50 subjects were on methadone maintenance and the remaining 28 subjects were "street addicts" using illicit methadone or heroin. For the methadone maintenance patients, level of dependence ranged from 5 to 40 mg methadone per day, with a mean of 19 mg. Street addicts using illicit methadone were stabilized on 5-30 mg methadone (mean of 19 mg) for approximately two weeks prior to starting detoxification while those using heroin

(range: $10-150 per day; mean: $52 per day) were switched directly to clonidine without iterim stabilization on methadone.

From the levels of dependence specified above there was a simultaneous abrupt discontinuation of opiates and introduction of clonidine. For the methadone-dependent subjects, placebo methadone was introduced on the first day of clonidine treatment and administered daily for the remainder of the detoxification procedure. For all subjects, the method of clonidine induction was the same as that described above for the gradual detoxification procedure. The maximum daily dose of clonidine ranged from 0.2 to 0.9 mg, with a mean of 0.5 mg/day. Ten days after opiates were discontinued, a naloxone challenge of 1.2 mg i.v. was administered to confirm opiate-free status in preparation for immediate induction onto naltrexone. After the second day on naltrexone, clonidine was discontinued gradually by 0.1 or 0.2 mg decrements per day until a zero dose was reached.

RESULTS

Clinical Outcome

A major aim of these clinical trials was to obtain a preliminary assessment of clonidine's efficacy as a transitional treatment to bridge the gap between opiate dependence and naltrexone, and the relevant outcome data are presented below in Table 2.

Table 2

DETOXIFICATION SUCCESS RATES FOR SUBJECTS IN THE GRADUAL AND RAPID DETOXIFICATION GROUPS

	Naltrexone Starters	Non-Starters
I. GRADUAL DETOXIFICATION GROUP (N=20)	10/20 (50%)	10/20 (50%)
II. RAPID DETOXIFICATION GROUP (N=50)	35/50 (70%)	15/50 (30%)
A. Methadone patients (N=22)	18/22 (82%)*	4/22 (18%)
B. Street Addicts (N=28)	17/28 (61%)	11/28 (39%)
1. On Heroin (N=11)	4/11 (36%)	7/11 (64%)
2. On Methadone (N=17)	13/17 (76%)**	4/17 (24%)

* Street addicts vs methadone maint. patients: $x^2 = 2.61$, df=1, $p > .10$
** Heroin vs methadone street addicts: $x^2 = 4.46$, df=1, $p < .05$

Subjects who completed detoxification and received at least one dose of naltrexone are categorized as "naltrexone starters" and those who failed to complete detoxification are categorized as "nonstarters".

Table 2 shows that of the 20 subjects who underwent the gradual detoxification procedure, 50 percent started naltrexone. In light of the earlier findings of significantly attenuated withdrawal symptoms after a single dose of clonidine, this 50 percent success rate was somewhat disappointing. Although the adjunctive clonidine suppressed withdrawal symptoms that emerged from successive decrements in meth-

adone, when daily methadone doses finally reached zero milligrams, clonidine's ability to suppress symptoms seemed markedly reduced. The procedure in which methadone was abruptly discontinued appeared to circumvent this problem as reflected by the greater success rates, as shown in Table 2. Among the 50 subjects in the Rapid Detoxification group, 70 percent started naltrexone and only 30 percent failed to complete the detoxification procedure. A breakdown of these 50 subjects revealed a greater success rate for methadone maintenance patients (82%) as compared with street addicts (61%), although this difference was not statistically significant. A further breakdown of the street addict subgroup into heroin vs methadone users reveals that 76 percent of the methadone users started naltrexone as compared with only 36 percent of the heroin users, a statistically significant difference.

In an attempt to account for these outcome differences, a retrospective analysis of mean level of opiate dependence was performed for naltrexone starters vs nonstarters in each of the subject groups and the results are presented in Table 3.

Table 3

MEAN PREDETOXIFICATION LEVEL OF OPIATE DEPENDENCE FOR NALTREXONE STARTERS AND NONSTARTERS

	Naltrexone Starters	Nonstarters
I. Gradual Detoxification	16 mg	18 mg
II. Rapid Detoxification		
A. On Methadone	26 mg	23 mg
B On Heroin	$21	$70*

* Wilcoxon Rank Sum Test: W=12, $p < .05$.

These data show no significant differences in level of dependence between naltrexone starters and nonstarters except for heroin users where a high level of dependence was associated with poor outcome.

Clonidine Effects

Most subjects reported that clonidine reduced but did not completely eliminate their withdrawal symptoms. The symptoms reduced most effectively and consistently by clonidine were chills, lacrimation, rhinorrhea, yawning, stomach cramps, sweating and muscle/joint aches. Marked reductions in anxiety and restlessness were also reported. Although clonidine substantially alleviated withdrawal distress, none of the 70 subjects reported that clonidine induced euphoria or any of the other subjective effects of opiates. Clonidine's lack of opiate-like subjective effects was reflected by the fact that subjects on clonidine easily detected the blind transfer from active to placebo methadone prior to the emergence of withdrawal symptoms.

Clonidine side effects consisted of sedation, dry mouth, and decreased blood pressure. Sedation from clonidine had both positive and negative aspects. Nighttime doses helped alleviate insomnia but morning and afternoon doses exacerbated symptoms of anergia and weakness leading to complaints of interference with daytime functioning. After at least several days of daily administration, tolerance developed to clonidine's sedative effect and additional nighttime sedation was required in approximately 50 percent of subjects who went on to complete the detoxification process. Blood pressure values decreased from a mean of 120/80 preclonidine to 105/68 at the maximum daily dose ($\bar{X}$=0.7 mg). Only 6 subjects reported symptoms of orthostatic hypotension such as dizziness or lightheadedness upon standing.

Abrupt discontinuation of clonidine after 2-6 weeks of daily administration and at least 2 days on naltrexone produced complaints of headaches and exacerbated withdrawal symptoms of chills, sweating, nervousness and muscle/joint aches. In some subjects, blood pressure values temporarily increased above preclonidine levels but there was no evidence of a clinically significant rebound hypertension. Experience with varying rates of clonidine dosage decrements indicated that the least problematic method consisted of 0.1 or 0.2 mg decrements per day until a zero dose was reached. This method resulted in no headaches, re-emergence of withdrawal symptoms, or abnormally elevated blood pressure values.

DISCUSSION

The present study confirms the single-dose findings of Gold et al. (1978) and demonstrates the safety and feasibility of clonidine detoxification in an outpatient clinical setting. Although conclusions about clonidine's efficacy in these preliminary open clinical trials are limited by the absence of an appropriate control group, comparison with reports of other investigators using routine detoxification procedures suggests that clonidine enabled patients to abruptly discontinue opiates and remain opiate free long enough to initiate treatment with naltrexone. For example, the 1978 report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists shows that only 21 percent of methadone maintenance patients and 17 percent of street addicts reached zero methadone and remained opiate free long enough to begin naltrexone treatment. Senay et al. (1977) reported that 53 percent of methadone maintenance patients detoxified by gradual methadone decrements reached a zero dose and remained abstinent for at least one week. These figures are substantially lower than the success rates of 82 percent for methadone maintenance patients and 61 percent for street addicts in the present investigation. It can also be said on the basis of clinical experience that abrupt discontinuation of as much as 40 mg chronic methadone would have had little chance of a successful outcome without the aid of clonidine.

Although it was expected that the use of clonidine in normotensive outpatients might be seriously hampered by problems of orthostatic hypotension, this was not the case. The low incidence of such untoward side effects can be attributed primarily to our conservative

dosing practices and close daily monitoring of each patient's clinical course. Clonidine's lack of opiate-like subjective effects limits its abuse potential among addicts, but it might be abused in attempts at self-medication for withdrawal symptoms. This could result in severe hypotension from clonidine overdose or rebound hypertension from discontinuing clonidine abruptly.

Clonidine's paucity of adverse side effects, lack of euphorogenic properties, and significant attenuation of withdrawal symptoms, point to its potential usefulness as a safe and effective treatment for opiate withdrawal. However, the present experience indicates that controlled clinical trials are needed before definitive conclusions can be drawn about clonidine's efficacy in opiate detoxification. A study of this type is currently in progress at New York Medical College. If thesecontrolled trials confirm the current optimism about clonidine, a greater number of addicted individuals might be successfully withdrawn from opiates and given the option of other treatment modalities such as naltrexone.

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Usefulness of Propoxyphene Napsylate for Maintenance Treatment of Narcotic Addiction

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Recently several studies have examined the use of propoxyphene napsylate (Darvon-N) in the detoxification and maintenance of narcotic addicts. Tennant (1974) reported that three programs in Los Angeles had succeeded in detoxifying 280 heroin addicts with propoxyphene napsylate, while maintaining 92 others on an outpatient basis for periods up to 240 days. In a doubleblind detoxification study comparing propoxyphene napsylate and methadone, he found that propoxyphene patients were more likely than methadone patients to be opiate abstinent at one month followup (Tennant, Russell, Casas, 1975).

However, in this doubleblind study, Tennant found propoxyphene to be less effective than methadone in suppressing withdrawal complaints. He also noted side effects from propoxyphene, such as mild visual hallucinations, slurring of speech and seizure-like symptoms (Tennant, 1974, 1973). Jasinski (1977) reported that propoxyphene napsylate used in maximum non toxic doses (about 1200 mg per day) produced narcotic-like activity equal to that of only 20 to 25 mg of subcutaneously administered morphine, or 10 mg of orally administered methadone. Again, he found that propoxyphene napsylate doses greater than 700 mg produced disturbing side effects in many subjects.

This paper will report the results from two studies, one carried out in Los Angeles and one in Philadelphia. Both were designed to evaluate the usefulness of propoxyphene napsylate in the maintenance treatment of opiate addiction. In both studies, propoxyphene was prescribed in divided doses. This allowed patients to receive the higher amounts required for maintenance that would have been toxic in a single dose. The protocols followed by the two clinics were similar, thus allowing data to be pooled.

METHODS

At each location, addicts applying for methadone maintenance

treatment between the ages of 19 and 55 with "mild to moderate" opiate habits were selected. Those with larger habits, who were expected to require more than 30 mg methadone, were excluded. An ample number of patients was available, because the average daily methadone dose was 35 mg in each clinic. Current physical dependence was verified by signs of abstinence and use. Patients with psychoses, seizure disorders, hepatitis, severe liver disease, or any other serious illness were excluded. Approval from the Food and Drug Administration (FDA) was obtained for a waiver of the two year minimum addiction requirement for methadone maintenance, so that patients who had been addicted for six months or more were eligible for treatment in the experimental programs. Individuals were allowed to remain in the study for a maximum of six months. A double blind format insured that neither patients nor therapists were informed about the individual's experimental group.

Both medications were prepared in capsules that were identical in taste and appearance. Medicines were prescribed in divided doses, to be taken in the clinic, and at home approximately 12 hours later. The maximum dose of methadone was 36 mg per day, all of which was ingested at the clinic (takehome doses for the methadone group were placebo). This design was arranged by consultation with the FDA, the Drug Enforcement Administration (DEA), the National Institute on Drug Abuse (NIDA), and both research groups. It was a compromise intended to prevent methadone diversion while allowing propoxyphene to be prescribed in divided doses, in order to minimize its side effects and maximize its therapeutic effectiveness.

The protocol was explained to all prospective candidates and informed consent was obtained. All had the option of choosing any other form of treatment offered at the clinic. In Philadelphia, before signatures were accepted a short quiz was given to assure full understanding of all items included in the consent form.

Patients in each study were given a complete physical examination, including chest x-ray, CBC, urinalysis, SMA-6/12, EEG and EKG. A Beck Depression Inventory, a symptom check list, and a narcotic withdrawal scale were also done. The physical examinations, including laboratory tests, were repeated at two weeks, and monthly, until termination. The EKG was administered at three months and six months. The chest x-ray and EEG were repeated at termination. Vital signs and urinalyses for drug screening were collected weekly. Patient and counselor reports of employment, personal adjustment, and criminal activity were given weekly. The Philadelphia group also gave a Brief Psychiatric Rating Scale, Hamilton Anxiety and Depression ratings. Gordon Personality Profile, Wonderlic I.Q. test, anxiety checklist, and a sentence completion test at intake, one month, three months, and six months (or termination). All physical and psychological measures taken during the study were done 24 hours after the patient received his last medication.

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One hundred and twenty-seven patients received propoxyphene (79 in Philadelphia, 48 in L.A.) and 103 patients were treated with methadone (68 in Philadelphia, 35 in L.A.). Methadone patients who reached the maintenance state of treatment were stabilized on an average of 32 mg per day, while propoxyphene patients stabilized on 1000 mg per day.

RESULTS

The characteristics of the Los Angeles and Philadelphia samples at intake are summarized in Table I. As can be seen, the samples differ significantly with regard to racial and sexual composition and in terms of educational and legal status at intake. Differences in background and drug history were also compared between medication groups for each of these samples, and no statistically significant differences were found.

Physical examinations were completed on all patients at the start of treatment. Results indicated no significant differences between the two medication groups. Serial EEGs and laboratory analyses were performed during the study. EEG results for both groups showed the increases in high frequency, lower voltage activity typically found in people taking psychotropic drugs, and no patient had an epileptic seizure during treatment. Laboratory test results indicated that SGOT levels in the methadone clients were elevated at intake and decreased to normal levels during the study. In the propoxyphene group bilirubin values decreased from high normal to mid normal levels during treatment. Serious toxicity was absent in both groups despite relatively long treatment duration (average six weeks) and is discussed in more detail elsewhere (Woody, Tennant, McLellan, this volume).

Duration of treatment is summarized in Table II. Patients were divided into short term (less than one month) and long term (more than one month). In both studies, methadone patients tended to stay in treatment longer than propoxyphene patients. In Philadelphia this finding was significant at the .01 level. In Los Angeles, although results were not significant, they were in the same direction.

Treatment was divided into three periods: Induction (first four weeks), Maintenance (from week five until detoxification or termination), and Detoxification (until detoxification was complete or allotted treatment time ran out). A wide variety of physical symptoms and drug side effect data were examined and analyzed for each patient. Propoxyphene patients reported more symptoms, and greater symptom severity, than methadone patients during the Induction period, but these results were only significant for the Induction period in the Philadelphia study, although the Los Angeles results were in the same direction. These physical symptoms were usually related to withdrawal rather than side effects of propoxyphene itself. For example, in the Philadelphia study propoxyphene patients reported more difficulty sleeping,

greater anxiety or nervousness, and heightened irritability.

During the Maintenance period, overall indices of symptoms and their weighted severity scores did not distinguish between medication groups in either study. So few patients reached Detoxification stage (4 propoxyphene and 8 methadone patients in Los Angeles; 2 propoxyphene and 11 methadone patients in Philadelphia) that statistical tests were not meaningful.

One of the most important measures taken from each patient was the weekly urinalysis. Urine was tested for the presence of various illicit street drugs, and especially for evidence of morphine. Among short term patients in both studies, propoxyphene and methadone groups did not differ in frequencies of positive urines. Among long term patients, however, an examination of the pooled data shows that 64% of the propoxyphene patients had positive urines for at least half of the weeks tested, while among methadone patients, the comparable proportion was 41%. These results are significant at the $p < .05$ level ($X^2 = 4.0$, $df = 1$). Use of amphetamines and barbiturates was infrequent and did not differ between medication groups.

Counselor reports of social adjustment were also analyzed and no differences were found between medication groups in either study. The most important factor in predicting vocational adjustment was pretreatment employment status; those employed before treatment tended to remain employed. Ratings of psychological adjustment were obtained for long term patients in both studies. Medication groups differed only on ratings of apathy (propoxyphene patients showed more apathy).

Reasons for termination were coded into categories based upon their positive (completion of treatment, detoxification), negative (medications not working, extended absence), or neutral (jail, scheduling problems) implications for effectiveness of the treatment medication. The distribution of patients' reasons for termination are presented by these codes for both the propoxyphene and methadone patients in Table III. The data for both the Philadelphia and Los Angeles samples are combined in the table as there were no statistically significant differences between them. Thirty percent of the methadone patients terminated for positive reasons, 57% for negative reasons, while 13% terminated for reasons unrelated to the medications. The comparable figures for the propoxyphene groups were 13%, 75%, and 12%. These distributions of answers differ significantly ($p < .01$) between the two groups.

Followup interviews were scheduled for both samples at one month following treatment and additionally at six months in the Philadelphia sample only. Patients were interviewed extensively concerning drug use, living arrangements, physical and psychological well being, vocational and crime data, and benefits from treatment. Patients' urine samples were also collected.

An average of 85% of the eligible patients were contacted in both clinics at the one month interval and results were examined separately for the two samples. No significant differences between methadone and propoxyphene patients were found in either sample, although patients in both treatment groups reported less drug use than at intake. Results of the six month followup at Philadelphia produced similar findings, showing no significant differences in posttreatment adjustment between the two groups. Approximately 22% of the patients in each treatment group were drug free (by urine and interview) at that time.

COMMENTS

Our findings indicate that propoxyphene is a less satisfactory medication than methadone for maintenance treatment of narcotic addiction. Propoxyphene patients tended to drop out of treatment earlier, and those who did remain in treatment one month or longer were more likely to terminate for a reason which indicated poor progress. Propoxyphene patients tended to drop out early. Those who stayed in treatment longer than one month were more likely to abuse heroin. The early dropout rate of propoxyphene patients usually was related to higher withdrawal symptom complaints during the first four weeks of treatment. A small number of propoxyphene patients dropped out due to signs and symptoms of CNS irritability. This finding is consistent with the reported side effects of high dose propoxyphene (Tennant, 1973; Jasinski, Pernick, Clark, 1977). However, side effects were relatively minor due to the divided dose schedule for propoxyphene used in both studies.

We note that to some degree the validity of these conclusions may be a function of local conditions, such as the availability of methadone treatment. In the Philadelphia study, patients had immediate access to methadone treatment after termination from the study. In that setting, about three-fourths of the patients treated with propoxyphene dropped out within one month. Some patients left the clinic, while others switched to methadone maintenance. However, despite these short term differences, follow-up data indicated that posttreatment adjustment between treatment groups did not differ.

TABLE I

Intake Data

	Philadelphia	Los Angeles	Sig.
Males	99%	85%	*
Mean Age	28.6	29.8	N.S.
Race			
% Black	71%	0%	
% White	29%	44%	*
% Mexican-American	0%	56%	
H. S. Graduates	71%	43%	*
Unemployed	59%	70%	N.S.
Current Legal Problems	43%	28%	*
Mean Years Addicted	7.3	8.3	N.S.
Prior Drug treatments	2.1	1.5	N.S.

* = $p < .01$ (x^2)

TABLE II

Duration of Treatment

	Philadelphia		Los Angeles	
	Propox.	Meth.	Propox.	Meth.
	N (%)	N (%)	N (%)	N (%)
LONG TERM (1 month or more)	22 (28)	38 (55)	36 (78)	30 (88)
SHORT TERM (Less than 1 month)	57 (72)	30 (45)	10 (22)	4 (12)
	$x^2 = 11.9$	$p < .01$	$x^2 = 1.34$	$p < .10$

TABLE III

Termination Reasons
(Philadelphia & Los Angeles Combined)

	Propoxyphene	Methadone
Positive reasons	16 (13%)	31 (30%)
Completion	6	10
Detox	10	21
Negative reasons	94 (75%)	59 (57%)
Transfer to Meth. Maint.	4	5
Side effects	15	14
Meds not holding	20	14
Absence	55	26
Unrelated to Med.	16 (12%)	13 (13%)
Jail	10	8
Schedule Probs.	6	5
	N = 126*	N = 103

$x^2 = 11.2$ df = 2 $p < .01$

*Reasons for termination on one propoxyphene patient were not known.

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Management of Neonatal Narcotic Abstinence Utilizing a Phenobarbital Loading Dose Method

Finnegan, L. P.; Mitros, T. F.; Hopkins, L. E.

The suggested therapy for the neonatal abstinence syndrome has been phenobarbital, paregoric, chlorpromazine, and diazepam. The choice of a particular agent and its dosing regimen has been based on individual clinical experience and subjective clinical assessment of symptomatology (Nathenson, Golden, and Litt 1971; Reddy, Harper, and Stern 1971; Zelson, Rubio, and Wasserman 1971). At present, little information is available about the dose response curves, pharmacokinetics, or inter-, intra-individual patient variability of pharmacokinetics when these agents are administered to the newborn.

It was our intent to examine the feasibility of administering an oral loading dose of phenobarbital, to observe the consistency of serum levels obtained from such an oral loading dose, and to test the possible clinical application of such a regimen.

Of these four agents, phenobarbital has been most extensively studied in the newborn during management of seizures and prophylaxis of hyperbilirubinemia (Jalling 1975; Pearce, Sharman, and Forster 1977). Several studies have reported a correlation between a loading dose administered either orally or parenterally and the peak serum concentration (Brachet-Liermain, Goutieres, and Aicardi 1975; Viswanathan, Booker, and Welling 1978). The amount of phenobarbital measured in the serum at the time of maximum concentration has been found to be roughly 1.3 times the dose administered parenterally, and this peak concentration was somewhat lower in relation to the dose administered orally (Viswanathan, Booker, and Welling 1978). Further, the time of peak serum concentration has been found to occur from 30 minutes to 4 hours after administration of a loading dose (Brachet-Liermain, Goutieres, and Aicardi 1975; Jalling 1975; Pearce, Sharman, and Forster 1977; Viswanathan, Booker, and Welling 1978).

We postulated that these results may have direct application to the treatment of neonatal abstinence due to in utero exposure to psychotropic drugs. In our preliminary studies, more rapid control of withdrawal symptomatology could be attained by the

administration of an oral loading dose of phenobarbital, when compared with the conventional dosing method, in order to achieve a therapeutic serum level of this agent within four hours of administration. The therapeutic serum level recommended in the control of neonatal seizures has been 15 to 40 micrograms per milliliter.

This paper will describe the use of an oral phenobarbital loading dose approach in conjunction with a clinical scoring system used to monitor and manage withdrawal symptomatology as seen in the neonatal narcotic abstinence syndrome.

METHODS

Nineteen consecutive neonates with the narcotic abstinence syndrome were studied. There were 13 males and 6 females. Birth weights ranged from 1.96 to 3.99 kg. These neonates were born to mothers maintained on methadone but who also occasionally took a variety of psychotropic agents in various quantities throughout their pregnancy. Neonates were admitted to the Intensive Care Nursery and evaluated for narcotic abstinence symptoms using a scoring system developed at our hospital which has been patterned after our initial scoring system which has been previously presented (Mac New, Mitros, and Finnegan 1978) and published (Finnegan et al. 1975) [Table 1].

The abstinence score is comprised of twenty-one of the most commonly seen symptoms in the passively addicted neonate. Signs are recorded as single entities or in several categories if they occur in varying degrees of severity.

Each symptom and each degree of severity of each symptom has been assigned a score. The higher scores were given to signs or symptoms which are associated with increased morbidity and mortality. The total score for the specified time interval of measured infant behavior is added and recorded at the bottom of the scoring sheet.

It should be emphasized that the scoring system is dynamic rather than static, that is, all of the signs and symptoms observed during the two or four hour time intervals in which infant symptomatology is monitored are point-totalled for that interval.

The infants were assessed for withdrawal symptomatology at two-hour intervals for the first forty-eight hours of life, then every four hours thereafter. If, at any point, the infant's total score was 8 or greater, every two-hour scoring was initiated and continued for twenty-four hours from the last total score of 8 or greater. If the two-hour scores continued to be 7 or less for twenty-four hours, then four-hour scoring intervals were resumed.

The need for pharmacologic intervention was indicated when the total abstinence score was 8 or greater for three consecutive scorings or when the average of any three consecutive scores was 8

Table 1

NEONATAL ABSTINENCE SYNDROME ASSESSMENT AND TREATMENT

SYSTEM	SIGNS AND SYMPTOMS	SCORE
CENTRAL NERVOUS SYSTEM DISTURBANCES	Excessive High Pitched (Or Other) Cry	2
	Continuous High Pitched (Or Other) Cry	3
	Sleeps < 1 Hour After Feeding	3
	Sleeps < 2 Hours After Feeding	2
	Sleeps < 3 Hours After Feeding	1
	Hyperactive Moro Reflex	2
	Markedly Hyperactive Moro Reflex	3
	Mild Tremors Disturbed	1
	Moderate-Severe Tremors Disturbed	2
	Mild Tremors Undisturbed	3
	Moderate-Severe Tremors Undisturbed	4
	Increased Muscle Tone	2
	Excoriation (Specify Area):_____	1
	Myoclonic Jerks	3
	Generalized Convulsions	5
METABOLIC/VASOMOTOR/ RESPIRATORY DISTURBANCES	Sweating	1
	Fever < 101 (99-100.8°F./37.2-38.2°C.)	1
	Fever > 101 (38.4°C. and Higher)	2
	Frequent Yawning (> 3-4 times/interval)	1
	Mottling	1
	Nasal Stuffiness	1
	Sneezing (> 3-4 times/interval)	1
	Nasal Flaring	2
	Respiratory Rate > 60/Min.	1
	Respiratory Rate > 60/Min. with Retractions	2
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1
	Poor Feeding	2
	Regurgitation	2
	Projectile Vomiting	3
	Loose Stools	2
	Watery Stools	3
	TOTAL SCORE----------	

or greater. If the infant's total score was 12 or greater for two consecutive intervals or the average of any two intervals was 12 or greater, therapy was initiated. Therefore, all infants who met the scoring criteria for pharmacologic intervention were treated with phenobarbital no longer than 4-6 hours following the onset of significant symptomatology.

Eighteen of nineteen infants met the criteria for initiation of therapy, and therefore were given an oral loading dose of 16 mg/kg of sodium phenobarbital to rapidly achieve an expected therapeutic serum level of 18 mcg/ml. The sodium phenobarbital was in 60% propylene glycol solution containing 20 mg/ml to decrease the volume of solution and to maintain solubility and stability. Doses were administered with no relation to feedings. Serum samples were drawn by heel stick at 3, 12, and 24 hours after the initial loading dose and daily thereafter. Serum analysis was accomplished using the EMIT technique--an enzyme-multiplied immunoassay which is highly specific, rapid, and requires small volumes of serum.

If the total withdrawal score was less than 8 after the desirable therapeutic serum level was achieved, that level was maintained for 72 hours. Subsequent dosing was considered as "maintenance." A daily maintenance dose of 4-6 mg/kg/day was initiated 24 hours following the loading dose. The infants were started with 5 mg/kg/day for maintenance and then the dose was adjusted as necessary to maintain the desired serum phenobarbital level.

After 72 hours of maintenance, detoxification was begun; that is, the phenobarbital serum levels were allowed to decline at a rate of 10-20%/day, by administering phenobarbital 2 mg/kg/day. If serum phenobarbital levels indicated that detoxification was too rapid (that is, greater than 20%/day), the maintenance dose was increased to 3 mg/kg/day. If detoxification was too slow (that is, less than 10%/day), the maintenance dose was decreased by 1 mg/kg/day.

Once the serum levels fell below 14 mcg/ml and the total withdrawal score was still less than 8, the detoxification dose was decreased by 1 mg/kg/day. Once the serum level fell below 10 mcg/ml, and the total withdrawal score was less than 8, the phenobarbital was discontinued. The infant was observed for withdrawal symptomatology for 72 hours following discontinuation of therapy, then discharged if no symptoms reappeared.

If the total withdrawal score was greater than 8 after our desired therapeutic level was achieved, an attempt was made to increase the phenobarbital serum levels by 10 mcg/ml increments per 24 hour period until: (1) the total withdrawal score was less than 8 or, (2) the serum level reached 50 mcg/ml.

If the total serum phenobarbital level reached 50 mcg/ml or greater and the total withdrawal score was still greater than 8, then the choice of detoxicant therapy was reevaluated before

attempting to exceed the level.

Detoxification was carried out in the same manner as described previously. All infants had vital signs (heart rate and respiratory rate) taken every hour for six hours following the initial loading dose of phenobarbital. After six hours, the vital signs were taken at four-hour intervals until 24 hours following the loading dose, then routine monitoring was resumed.

Once the infant was controlled (that is, the total withdrawal score less than 8), then the phenobarbital serum levels were drawn daily immediately preceding the daily phenobarbital dose until therapy was discontinued (that is, when the total serum level fell to less than 10 mcg/ml).

RESULTS

Analysis of the data revealed that: seventeen of the eighteen infants were controlled when phenobarbital levels were between 20 and 30 mcg/ml. The loading dose of 16 mg/kg of sodium phenobarbital produced average daily blood levels at 24 hours of 17.4 mcg/ml with a standard deviation of 3.15 mcg/ml. No infant had blood levels above 25 mcg/ml with the loading dose while two infants had subtherapeutic levels of 11.5 and 12.8 mcg/ml 24 hours after the dose. No infant exhibited signs of toxicity or undue depression during the administration of the loading dose. The range of maintenance doses necessary to deal with metabolism and pharmacologic response aspects varied between 2 and 8 mg/kg/day.

In comparison to a conventional three times per day dosing regimen used previously, it was evident that therapeutic levels were obtained 15 to 24 hours earlier. In those infants not controlled by the usual 20-30 mcg/ml, the aggressive approach proposed allows higher serum levels to be obtained 40 to 72 hours sooner than under the conventional system.

One infant was not controlled with serum levels of 50 mcg/ml of phenobarbital. This infant's mother was on the largest methadone maintenance dose of 80 mg/day. Three of the four infants, born to mothers on doses of methadone greater than 35 mg/day, demonstrated an initial control of symptoms by phenobarbital in the first week of therapy only to relapse with higher scores that indicated more severe abstinence.

The latter four infants were hospitalized for an average of 43 days with a range of 22-55 days. The fourteen infants exposed in utero to methadone doses of 20 mg/day or less were hospitalized for an average of 26 days with a range of 13-46 days.

An advantage of this regimen is the maintenance dose approach whereby the daily mg/kg dose approximates the drug eliminated by metabolism, therefore maintaining the lowest efficacious serum level. We also feel that detoxification based on gradually

declining serum levels with monitoring of patient withdrawal symptomatology is a pharmacologically sound and clinically efficacious method of treating the neonatal abstinence syndrome which avoids the problem of relapses from premature discontinuation of therapy while defining an endpoint when therapy is no longer required.

CONCLUSION

A group of eighteen infants which experienced the neonatal abstinence syndrome due to prenatal maternal use of methadone responded adequately to phenobarbital with control of symptoms. By administering the phenobarbital as an initial single loading dose and closely monitoring the blood levels, maintenance dosing could easily be adjusted for variables in infant metabolism and pharmacologic effect. By use of a multifactoral abstinence scoring system, the pharmacologic effects on clinically observed abstinence symptomatology could be closely monitored and correlated with the blood levels. Serum levels of 20-30 mcg/ml were adequate to control all but one infant. Tapering the blood level of phenobarbital to 10-12 mcg/ml and observing no scores over 8 for 72 hours identified the place in time where abstinence was no longer significant and the infant could be discharged without medication.

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Relative Analgesic Potency of Intramuscular Heroin and Morphine in Cancer Patients With Postoperative Pain: A Preliminary Report:

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Heroin (diacetylmorphine; 7,8-didehydro-4,5 alpha-epoxy-17-methyl-morphinan-3,6 alpha-diol diacetate ester), although not employed in the United States, has been used in some countries as the treatment of choice in controlling pain in patients with advanced cancer. Heroin has been judged to produce more intense euphoria than morphine (Ross 1944; Seevers and Pfeiffer 1936; Elliott et al. 1971), an attribute which has been considered a reason for its being the preferred drug of narcotic addicts and for having particular virtues in the management of intractable pain and suffering of terminal illness (Twycross 1974; Twycross 1975). Apart from differences in relative potency and time action (Reichle et al. 1962), morphine and heroin have been shown to be similar in most respects, so that the uniqueness of heroin's attributes has been questioned (Lasagna, Von Felsinger, and Beecher 1955; Smith and Beecher 1962; Fraser et al. 1961; Martin and Fraser 1961). Indeed, there is considerable evidence to suggest that heroin is rapidly hydrolyzed to monoacetylmorphine and morphine after drug administration (Jaffee and Martin 1975). Controlled comparisons of intramuscular heroin and morphine have been previously carried out in postoperative patients (Reichle et al. 1962), but controlled intramuscular assays have not yet been carried out in patients with chronic pain due to cancer.

The study reported here is the first in a series intended to provide more substantial information as to whether heroin has any unique attributes which morphine may not have in the treatment of patients with advanced cancer. The purpose of this initial study is to determine the relative analgesic potency of intramuscular heroin compared to morphine and to compare the treatment-related changes in mood and side effects at equianalgesic doses in cancer patients with postoperative pain.

METHODS

Intramuscular doses of heroin of 2 and 4 mg and 4 and 8 mg were compared with 8 and 16 mg doses of morphine in two series of double blind, twin crossover relative analgesic potency assays. The method of the assay has been previously described in detail (Houde, Wallenstein, and Rogers 1960; Wallenstein and Houde 1975). The

method and modifications employed in this particular study are briefly described below.

Study Design

Each twin crossover assay consists of a series of four treatment studies incorporating a lower and upper dose of the standard and the test drug. The ratio of doses of standard to test drug are varied from study to study. Each patient receives two doses, a lower dose of one drug and an upper dose of the other. Each block of four patients is balanced for drug, dose and order, and the assignment of patients to treatments within the block is randomized. On completion of each block, a sequential decision-making process is instituted to determine whether the next block should incorporate a lower or higher dose ratio of standard to test drug. The objective of this process is to obtain as much data as possible in the equianalgesic effect range of the two drugs.

Collection of Data

Patients with postoperative pain are selected on the basis of an evaluation of the cause of pain, the appropriateness of treatment with the study drugs and the ability of the patients to communicate with the observer. Patients are seen at hourly intervals and questioned about the severity of their pains. If the patient requests medication for pain and has not received an analgesic for at least three hours, and if the pain is reported as moderate or severe, a study drug is given by the nurse observer. Observations are then made at one half hour and continued at hourly intervals for six hours or until pain has returned to the premedication level. At each observation time, the patient is questioned as to the severity of pain, degree of pain relief, whether or not the pain has been at least half relieved and whether or not he considers the drug acceptable. Volunteered and observed side effects are also recorded.

Patients are also asked to complete visual analog scales (VAS) and mood questionnaires. VAS data are obtained at the same observation times as categorical (CAT) data. The patient is asked to mark 100 mm scales at the point on the line which best reflects how he feels between "Worst I Could Feel" and "Best I Could Feel" for the mood VAS, between "Least Possible Pain" and "Worst Possible Pain" for the pain VAS and between "No Relief of Pain" and "Complete Relief of Pain" for the relief VAS. The mm distance from the origin to the point marked is measured and taken as the VAS score in each case. At the time of drug administration and at 2 hours after drug, patients are requested to estimate their moods more specifically by use of a set of 15 contrasting word pairs. Patients are instructed to circle either a neutral, "0", point or a "1", "2" or "3" in the direction of either word of the pair. Negative feelings are later assigned negative signs and positive feelings, positive signs. The number is taken as the mood questionnaire score for each pair of words.

RESULTS AND DISCUSSION

Data from the first 36 patients who provided both complete CAT and VAS pain and pain relief scores are presented here. Analyses of variance for twin crossover assays were carried out with modifications for sequential study design (Finney 1964). The use of both CAT and VAS measurements allowed the calculation of eight estimates of relative potency: estimates based on peak CAT and VAS pain intensity difference, total CAT and VAS pain intensity difference and the four sets of corresponding pain relief data. Table 1 shows the results of the analyses in terms of relative potency (ϕ), upper and lower 95 percent confidence limits and lambda, a measure of the experimental efficiency of a bioassay. Lambda is derived by dividing the standard error by the common slope. The lower the value of lambda the greater the sensitivity of the assay.

Table 1. Relative analgesic potency of IM heroin vs. morphine.

	PAIN INTENSITY DIFFERENCE				PAIN RELIEF			
	Peak		Total		Peak		Total	
	CAT	VAS	CAT	VAS	CAT	VAS	CAT	VAS
ϕ	2.2	2.9	2.1	2.4	2.5	2.9	2.1	2.3
95% limits	10.5	5.2	3.3	5.3	3.0	5.1	2.9	3.3
	<0.1	1.9	1.1	1.0	1.6	1.8	1.5	1.5
Lambda	0.62	0.36	0.38	0.48	0.34	0.36	0.26	0.31

Potency estimates based on peak effects were consistently higher than those based on total effects, an indication that heroin has a shorter duration of action than morphine at equianalgesic peak effects. Estimates using VAS data were consistently higher than the corresponding CAT data estimates. The use of pain relief data provided more efficient estimates than use of pain intensity data. Comparable limits and efficiency were obtained with analyses using CAT and VAS data. These results show intramuscular heroin hydrochloride to be between 2.1 and 2.4 times as potent as morphine sulfate in terms of total analgesic effect and between 2.2 and 2.9 times as potent in terms of peak effect. Thus, approximately 4 mg of heroin and 10 mg of morphine are judged to be equianalgesic in relieving postoperative pain.

Time effect curves for heroin and morphine (not shown) also suggest that heroin has a shorter duration of effect than morphine. Table 2 shows the mean time (minutes ± standard error) of the peak intensity of VAS pain relief compared to the time of peak VAS mood for both drugs, and also shows the level of significance (two tailed, paired t-test) associated with the difference between the two means. A significant time lag is observed between peak pain relief and peak mood for both heroin and morphine. This may suggest that changes in mood may not be determined solely by the analgesic effect of these drugs.

Table 2. Time of peak intensity of pain relief and mood after IM heroin and morphine.

	DOSE ($\overline{mg}$)	RELIEF	MOOD	P<
Heroin.....	4.6	69 ± 7	90 ± 9	0.025
Morphine.....	11.1	86 ± 10	120 ± 13	0.005

Attempts were made to calculate estimates of relative potency in terms of mood, but it was observed that both the direction and degree of mood change after drug were highly dependent upon the initial mood of the patient. For example, the total VAS mood change (sum of the differences between hourly VAS mood scores and initial score) after 8 mg of heroin was inversely related to initial mood with a linear correlation coefficient of -0.84 ($P<0.001$). The linear regression line crossed the abscissa at an initial mood score of approximately 50 mm. That is, patients who initially report relatively low mood scores report positive changes after drug, whereas those patients who initially report high scores report negative mood changes after drug. Qualitatively similar results were obtained for the other doses of both drugs and examination of the word pair mood questionnaire data yielded similar results. The influence of initial mood requires further evaluation by covariance and multiple regression analyses before any quantitative and definitive statements can be made concerning the relative effects of heroin and morphine on mood.

When the patient population as a whole is considered, however, both heroin and morphine provide significantly improved moods. Table 3 lists the word pairs from the mood questionnaire each arranged according to negative mood on the left and positive mood on the right. To the right are the mean mood scores at the time of drug administration and at two hours after drug and the level of significance (two tailed, paired t-test) associated with the difference between the two means for both heroin and morphine. The word pairs are separated according to several categories. Prior to drug administration, patients report being somewhat restive; both heroin and morphine result in significant shifts toward feelings of tranquility. Prior to drug, patients reported being somewhat more euphoric than dysphoric; drug administration results in some significant shifts toward feelings of euphoria. Initially, patients were optimistic and these feelings were improved somewhat after drug. Drug administration also results in some positive shifts toward enthusiasm and feeling less serious.

Table 4 shows the side effect occurrence after heroin and morphine in all patients having received a test drug. The percentage of patients with side effects appears to be dose related for both drugs. The incidence of side effects is consistent with the relative analgesic potency estimates. The most prominent side effect observed or reported after both drugs was drowsiness. This effect and "relaxed" feelings were observed somewhat more frequently after morphine, whereas feelings of "high" and "euphoria" were reported slightly more frequently after heroin. However, the difference in occurrence of these effects were small and are of doubtful significance.

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Table 3. Word pair mood questionnaire scores before and after IM heroin and morphine.

FACTORS	HEROIN, $\overline{4.5}$ mg			MORPHINE, $\overline{11.9}$ mg		
I Agitation-Serenity	O Hr	2 Hr	P<	O Hr	2 Hr	P<
Shaky- Serene.....	-0.1	0.9	0.02	-0.8	1.3	0.001
Restless-Peaceful.....	-0.2	0.6	0.05	-0.6	0.9	0.005
Uneasy-At ease.....	-0.5	0.9	0.001	-0.4	1.1	0.005
Nervous-Calm.....	0.4	1.3	0.01	-0.2	1.3	0.001
II Dysphoria-Euphoria						
Blue-Cheerful.....	0.5	1.2	0.01	0.0	0.6	0.02
Angry-Contented.....	0.9	1.4	0.05	0.8	1.4	0.005
Sad-Happy.....	0.7	1.1	0.2	0.1	0.7	0.05
Alone-Sociable.....	0.0	0.8	0.05	-0.4	0.6	0.02
Don't care-Interested..	1.4	1.7	0.4	1.8	1.5	0.3
Pessimistic-Optimistic.	1.2	1.4	0.4	1.4	1.6	0.7
III Pessimism-Optimism						
Pessimistic-Optimistic.	1.2	1.4	0.4	1.4	1.6	0.7
Apprehensive-Confident.	0.9	1.1	0.6	0.4	1.2	0.01
Apathetic-Enthusiastic.	0.3	1.1	0.02	0.9	1.1	0.6
IV Apathy-Enthusiasm						
Heavy-Bouyant.....	-1.0	-0.1	0.001	-1.3	-0.6	0.05
Lethargic-Peppy.....	-1.2	-1.0	0.6	-1.4	-1.3	0.8
Apathetic-Enthusiastic.	0.3	1.1	0.02	0.9	1.1	0.6
V Serious-Amused.....	-1.2	-0.7	0.2	-1.1	-0.3	0.02

In summary, the results of this study in postoperative patients have, thus far, revealed little that was not expected from a review of the literature. Heroin hydrochloride appears to be about two to three times more potent than morphine sulfate as an analgesic, to act more promptly and to have a slightly shorter duration of action. There is a suggestion that heroin may have a somewhat different spectrum of side effects and mood effects compared to morphine, but the effects of both drugs on mood were inversely correlated with the patients' feelings at the time of drug administration. Regardless, as a group, patients responded to both drugs with significantly improved moods. A lag time between the peak intensity of analgesic and mood effects of both heroin and morphine suggest a dissociation between these effects. Whether or not these early impressions will be reinforced as this study proceeds, and whether or not the effects of the drugs in patients with chronic pain due to advanced cancer will be any different than in these patients with postoperative pain, remains to be seen.

Table 4. Side effect occurrence after IM heroin and morphine.

	MORPHINE		HEROIN		
SIDE EFFECTS	8 mg	16 mg	2 mg	4 mg	8 mg
Pain Injection Site.	1				
Nausea.....		2		1	1
Vomiting.....					1
Dry Mouth.....	5	4	2	5	4
Sweating.....	2	2			
Sleepy (Drowsy).....	13	18	4	11	13
Groggy (Dopey).....	1	1		1	1
Lightheaded.....	2	3	1	1	1
Dizzy.....	2	2		1	3
Weak (Tired).....	1	2		3	1
Nervous.....					1
Relaxed.....	6	6	1	2	4
Palpitation.....		1			1
Headache.....				1	1
Increased Pain.....	1	1	1	1	
Floating Feeling....		1			1
Feeling of Unreality.		1			
Disoriented (Confused).					1
High (spacey).....		1		1	3
Apathetic.....	1	1	1	1	
Carefree.....	1				
Unsteady.....	1				
Diplopia.....					1
Increased Appetite....					1
Euphoria.....				2	1
Hot.....					1
Calm.....					1
Vivid Dreaming.....		1			
Difficulty concentrating.....		1			
N (patients, meds.)..	27	27	8	24	21
Pts. with side effect	18	22	5	16	16
% with side effect...	67	81	63	67	76

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Clinical Analgesic Assay of Oral Zomepirac and Intramuscular Morphine

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Zomepirac (McN-2783-21-98), sodium 5-(p-chlorobenzoyl)-1,4 dimethyl-1H-pyrrole-2-acetate dihydrate, is a close analog of tolmetin sodium, a compound currently marketed for the treatment of rheumatoid arthritis. Its pharmacological profile indicates antiinflammatory, antiarthritic and analgesic activity. In the rat, it antagonizes kaolin and carrageenin-induced edema. While zomepirac is inactive in the "tail-clip" analgesic assay, it is effective in blocking acetylcholine-induced writhing in mice. On the basis of both animal data and early studies in man, zomepirac appears to be well tolerated and more effective than aspirin and other antipyretic and nonsteroidal antiinflammatory drugs for the control of pain (McNeil Laboratories 1977). This report represents preliminary data in a clinical analgesic assay of oral zomepirac and intramuscular morphine.

METHODS

Study Design

Two parallel assays of orally administered zomepirac and intramuscular morphine are being carried out in two patient groups, one assay in patients with post-operative pain, and one in patients with chronic pain due to cancer. The assay in post-operative pain is designed as a series of sequentially related twin crossover studies comparing 50 and 100, or 100 and 200 mg of oral zomepirac with 4 and 8, or 8 and 16 mg of intramuscular morphine sulfate. Utilizing the same doses, a complete crossover comparison of the two drugs is being carried out in patients with chronic cancer pain. Each assay consists of series of studies of four treatments each, in which a lower and upper dose of zomepirac is compared with a lower and upper dose of the standard, morphine. In the twin crossover assay each patient receives a lower dose of one drug and an upper dose of the other in a randomized order. In the complete crossover assay, each patient receives all four medications to be included in the analysis. Periodic decisions are made, based on the patients' reports of pain relief, to adjust the doses of either the standard or test medication up or down in order to obtain most of the data in the equianalgesic range of the two drugs.

Data Collection

Observations are made on patients by full time trained nurse-observers who question the patients about their pain and degree of relief after medication and record the patients' verbal subjective reports. Patients are seen hourly and the nurse observers administer the coded randomized test medications when pain is either moderate or severe. Patients are seen hourly for up to six hours by the observer and the patients' verbal reports of severity of pain and degree of relief are recorded by the observer on standardized forms. Patients are not questioned directly about side effects, but all observed and volunteered drug effects are recorded. Detailed descriptions of the methodology have been previously reported (Wallenstein and Houde 1975).

In addition to the conventional verbal reports, subjective measurements of pain and pain relief utilizing visual analogue scales (VAS) were obtained in most patients so that direct comparisons of assay sensitivity utilizing verbal and visual scales could be made. In particular, it was felt that VAS measurements might be found to be more sensitive for the measurement of peak drug effects than the more limited categorical verbal scales. The VAS consisted of 100 mm horizontal lines labelled from "least possible" to "worst possible" pain and from "no" to "complete" relief of pain. Patients were asked to mark in pencil the place on the scale that reflected how they felt at the moment. Measurements were made in millimeters from the left edge of the scale to the patient's mark. VAS data were obtained by the nurse observers at hourly intervals immediately after the verbal reports.

That narcotics in appropriate circumstances are capable of affecting mood is well accepted. The extent of the effects in hospitalized patients when the drugs are administered therapeutically for pain, however, remains an open question. The current study of zomepirac and morphine was employed as a vehicle for developing mood scales that would be brief and simple enough to administer repeatedly to sick patients with pain, and to provide a comparison of mood effects after a narcotic (morphine) and a nonnarcotic analgesic (zomepirac). A VAS scale and a 15 item self scoring word-pair questionnaire were employed for this purpose. The mood VAS was obtained hourly, and the questionnaire was completed prior to, and at two hours after drug administration.

RESULTS

Conventional Relative Potency Assay:

Crossover comparisons have been obtained thus far in 132 post-operative patients and 17 chronic pain patients. The analgesic results, in terms of total relief scores utilizing our traditional categorical scales, are summarized in Table 1. Our original expectations, based on animal and early clinical pharmacology, was that analgesic equivalence might be obtained in the range of doses of 4 and 8 mg of IM morphine and 100 and 200 mg of PO zomepirac and both the post-operative and chronic pain patients were initiated using these

doses. Results in the first series, as illustrated in Table 1, show zomepirac to be more effective, relative to morphine, than expected. Doses of the drugs were subsequently adjusted in both patient populations, and it was not until a third series in the post-operative patients, in which the zomepirac doses were lowered to 50 and 100 mg, that its analgesic effects were in the same range as 8 and 16 mg of IM morphine.

Table 1. Summary of total relief scores for 6 hours after morphine IM and zomepirac PO on all series for patients with postoperative pain and chronic cancer pain.

POSTOPERATIVE PATIENTS:

SERIES	I		II		III	
	Dose(mg)	Relief	Dose(mg)	Relief	Dose(mg)	Relief
Morphine, IM	4	5.2	4	3.3	8	9.4
Zomepirac, PO	200	8.5	100	9.9	100	10.4
Zomepirac, PO	100	9.4	50	8.6	50	6.4
Morphine, IM	8	6.8	8	6.8	16	8.5

CHRONIC PAIN PATIENTS:

SERIES	I		II	
	Dose(mg)	Relief	Dose(mg)	Relief
Morphine, IM	4	4.1	8	4.7
Morphine, IM	8	5.0	16	5.7
Zomepirac, PO	100	7.5	100	5.0
Zomepirac, PO	200	5.7	200	7.5

Relative potency analyses (Finney 1964) for both populations were carried out eliminating the first series in each in which the drugs were obviously not in the equipotent range (Table 2). A valid analysis was obtained for the post-operative patients indicating morphine IM to be about 5x as potent as zomepirac PO in terms of verbal total relief estimate although the confidence limits are rather wide. A valid relative potency estimate could not be calculated due to the small amount of data in the chronic patients.

The time effect curves for the post-operative patients are quite similar for the two drugs, (Figure 1) although there is some indication of a slower onset for zomepirac. In the chronic pain patients, zomepirac appears to have a longer duration of action than morphine which may be due to narcotic tolerance in these patients. The overall incidence of side effects was roughly the same for both drugs (Table 3). Sleepiness, nausea, dry mouth and feelings of weakness were observed after both drugs, but more patients were groggy, lightheaded and dizzy after morphine while dyspepsia and sweating were observed after zomepirac.

Figure 1. Time-effect curves for oral zomepirac and intramuscular morphine in a twin crossover comparison in patients with post-operative pain. Mean categorical pain relief (ordinate) is plotted against time in hours (abscissa).

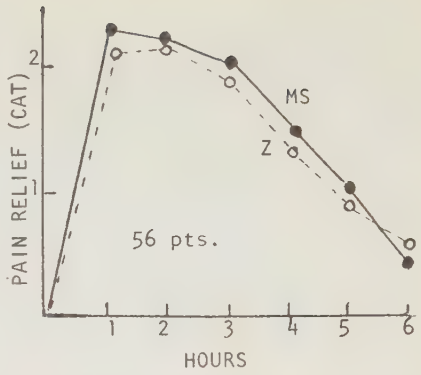

Table 2. Relative potency analysis of oral zomepirac and intramuscular morphine in patients with postoperative and chronic pain in terms of total categorical relief.

POST-OPERATIVE PAIN:

SOURCE	df	MS	F
Drugs	1	60.3	2.267
Slope	1	151.0	5.677*
Days	1	75.1	2.823
Days x Parellelism	1	7.0	
Within Pt. Error	76	26.6	
Parallelism	1	7.0	
Days x Drug	1	17.2	
Days x Slope	1	14.8	
Between Series	1	96.3	2.744
Among Pts. Error	76	35.1	1.320

β=6.77 ϕ=0.19 *P<0.05
λ=0.76 95% limits = 0.11, 1.5

CHRONIC PAIN:

SOURCE	df	MS	F
Among Patients	5	39.7	4.616*
Drugs	1	18.4	2.140
Slope	1	7.0	
Parallelism	1	3.4	
PxD Error	15	8.6	

β=2.91 ϕ=0.12 *P<0.05
λ=0.55 95% limits = ∞

Table 3. Side effect occurrence after intramuscular morphine given with an oral lactose placebo and after oral zomepirac given with an intramuscular saline placebo.

	MORPHINE, I.M.			ZOMEPIRAC, P.O.		
SIDE EFFECTS	4	8	16	50	100	200
Injection Site Pain	6	14	3	2		
Nausea	4	7	5	6	4	3
Vomiting			2		2	
Dyspepsia	2			1	2	3
Dry Mouth	6		4	1	3	4
Sweating	2		1	2	3	6
Tremors		1				
Flushed	1	1				
Itching		1				
Sleepy	13	36	19	11	19	25
Groggy	3	3	4	2	3	1
Lightheaded	3	2	3		2	
Dizzy	5	4	3		1	
Weak	3	2	5	2	8	5
Cold					1	
Nervous	1					
Relaxed		4		2	1	
Depressed						2
Crying						1
Dyspnea	1			1		1
Headache	5	3	2		3	4
Marked Increased Pain				1	3	4
Visual Hallucinations	1					
Disoriented	1	2	1			1
Blurred Vision		3			2	
Dreaming		1			1	
Euphoric	1		1		1	
More Alert					1	
Lethargic				2		
Singultus					1	1
Diarrhea					2	
Stomach Pain		1				1
Hot				1		
Shaky		1				1
Tingling Head				1		
Number of Patients	52	105	45	52	103	54
Patients with side effects	24	55	30	25	43	32
%Pts. with side effects	46	52	67	48	42	59

The confidence limits of the relative potency estimates are quite wide at this time, but this study is still in progress. At this point zomepirac would appear to be a surprisingly effective oral analgesic, capable of serving as a substitute for usual clinical doses of intramuscular morphine.

Visual Analogue Scales:

In order to compare the sensitivity and efficacy of the VAS with the standard categorical measures, analysis of variance and relative potency estimates in terms of peak and total relief were carried out in the twenty patients in Series III in whom both types of measures were obtained. The results of these analyses are summarized in Table 4. The estimates of relative potency (ϕ) obtained with both the verbal and visual scales were in reasonably good agreement; however, significant slopes and finite confidence limits were obtained in this small patient sample only with the measures of total and peak VAS relief. In terms of lambda (λ), an estimate of the efficiency of the assay arrived at by dividing the standard error by the slope, the analyses utilizing VAS were superior to those employing the categorical measures in this study. This limited data provides some evidence that VAS may be superior to categorical measures in small patient groups and, particularly, in terms of peak effect where the restrictions of a limited categorical scale may mask drug differences.

Table 4. Relative potency assays in the same patients employing either standard categorical or VAS relief scales.

		TOTAL RELIEF		PEAK RELIEF	
		CATEGORICAL	VAS	CATEGORICAL	VAS
MS	8 IM	8.4	227.0	2.7	72.4
MS	16 IM	8.4	232.0	2.6	64.8
Z	50 PO	5.8	133.7	1.9	45.6
Z	100 PO	10.8	324.2	3.0	88.4
	N	20	20	20	20
	β	8.3	325.2	1.7	58.5
	λ	0.67	0.43	0.56	0.36
	ϕ	0.16	0.16	0.12	0.15
	95% limits	∞	0.01,1.6	∞	0.05,0.35

Measurement of Mood:

The mood VAS, given hourly, and the questionnaire, given before and at two hours after drug, were found to be acceptable to the patients. Measurement of mood in patients taking medication for pain is complicated by the fact that the patient's pre-drug mood may vary, and the post-drug score is significantly influenced by the patients' starting mood. Nevertheless, analysis of covariance of the mood VAS indicates a significant positive drug effect with a relative potency of zomepirac to morphine of 0.18 (95% confidence limits = 0.08 to 0.93), which is in the same range as that obtained for pain relief. The mood VAS reflects a global patient response, and whether mood as measured using this parameter is a result of drug action or secondary to pain relief remains to be determined. In terms of the questionnaire, preliminary analysis indicates that selected word pairs(restless-peaceful, shaky-serene, and sad-happy) are most affected in the direction of improved mood by both drugs. Whether or not there is a differential drug effect remains to be

seen as additional data is obtained.

SUMMARY

Zomepirac appears to be an unexpectedly effective oral, non-opioid analgesic. The relative potency of oral zomepirac is roughly 1/5 to 1/8 that of intramuscular morphine. Visual analogues of pain relief offer a reliable alternative to verbal categorical scales, and may provide some advantages in assays of peak drug effect, and in relatively small patient populations.

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Conditioned Heroin Responses as an Indication of Readdiction Liability

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This study presents data on responses by drug addicts to stimuli associated with their drug-taking behavior. It also suggests a promising approach in developing an objective measure of a patient's likelihood of readdiction. The premise behind establishment of what we call a "Readdiction Liability Test" is the theory that conditioned responses by ex-addicts to heroin-related stimuli in the environment are a major cause of relapse (Wikler 1973). According to this thesis, encountering a person or place previously associated with drug-taking behavior will produce conditioned responses in ex-addicts similar to abstinence signs or craving. (The exact nature of these conditioned responses has not been precisely determined at this point). Evidence of this effect includes animal studies (Goldberg, Woods, and Schuster 1969; Goldberg and Schuster 1970; and Wikler 1965), anecdotal reports (Wikler 1973), and responses conditioned in the laboratory (O'Brien et al.1976). When the symptoms are elicited "in vivo" however, they are likely to lead to drug-seeking and-taking behavior. If this premise is correct, then one might expect addicts demonstrating the largest conditioned response or responding most readily to the appropriate heroin-related stimuli to have the greatest probability of readdiction. Finally, if these stimuli can be sufficiently isolated and recreated in the laboratory, where patients' responses (both psychological and physiological) can be monitored and quantified, then an objective measure of their responsivity can be established, and used as a guide to their readdiction liability.

In our laboratory we have begun to examine psychological and physiological responses in addicts to stimuli associated with their drug-taking behavior. The goal of our research has been to approximate the actual stimulus situation within the laboratory setting, and thus we hope to develop a "Readdiction Liability Test". Obstacles have included the inability or unwillingness of the addicts to participate in "guided imagery" as a method of recreating their own environment as well as our desire to have the subjects remain motionless to accurately monitor physiological responses.

In a previous study (Sideroff and Jarvik, in press) we described our initial procedures in obtaining conditioned responses in addicts

detoxifying from opiates. It was found that during a videotape (VT) showing heroin-related stimuli, the subjects (unlike control subjects) demonstrated a significant increase in heart rate and in number of galvanic skin responses (GSR). In addition, they had an increase in level of craving for opiates and increases in levels of anxiety and depression as measured by the Multiple Affect Adjective Checklist (MAACL).

The present study was designed to improve on the procedures and look at additional physiological response systems. In the procedure, we now allow for instantaneous indication of level of craving versus previously asking for level before and after the entire experiment. If the conditioned responses elicited in the laboratory are of a reduced level and shorter duration than on the street (due to the inappropriate context) a more immediate measure of craving is important.

METHOD

Subjects

Twelve volunteers from the Substance Abuse Service were used as experimental subjects. At the time of their participation nine were detoxifying from heroin (five were at 0 mg. methadone, two were at 2 mg., and two were at 5 mg.) and three were on methadone maintenance (one at 30 mg., and two at 60 mg. of methadone). Ten control subjects were volunteers from the nursing service of the Brentwood Veterans Administration Medical Center. They were used to control for the shock of viewing needles and injections. After being read the procedures, all subjects gave their written informed consent and were told they could withdraw from the experiment at any time.

Procedure

Subjects were asked to sit in a chair in front of a television monitor. They were then connected to a Beckman Dynograph via electrodes to record heart rate and GSR, as well as thermocouplers attached under the nose to monitor respiration and to the thumb for skin temperature. They were then given the MAACL; a brief drug history, and the Profile of Mood States (POMS). They were also given blank paper and a black magic marker and asked to draw a person. This was a projective technique we hoped would yield a sensitive measure of change in mood state; one that the subject would be unable to manipulate. This same series of tests was again administered to the subject at the conclusion of the experiment.

After completion of the questionnaires, the subjects were asked to relax. At this point they were shown a dial next to their right arm with the numbers 1 - 10 inscribed on the circumference. They were asked to dial the knob to their level of craving for heroin, with '0' indicating "no desire" and '10' being "total desire". Additional instructions helped the subjects establish a frame of reference to determine their craving level. They were instructed to change that level any time during the experiment at which their

level of craving actually changed. In addition, they were asked to check the dial just prior to each trial to ascertain whether it was set correctly. Trials were preceded by a three-second tone as a cue.

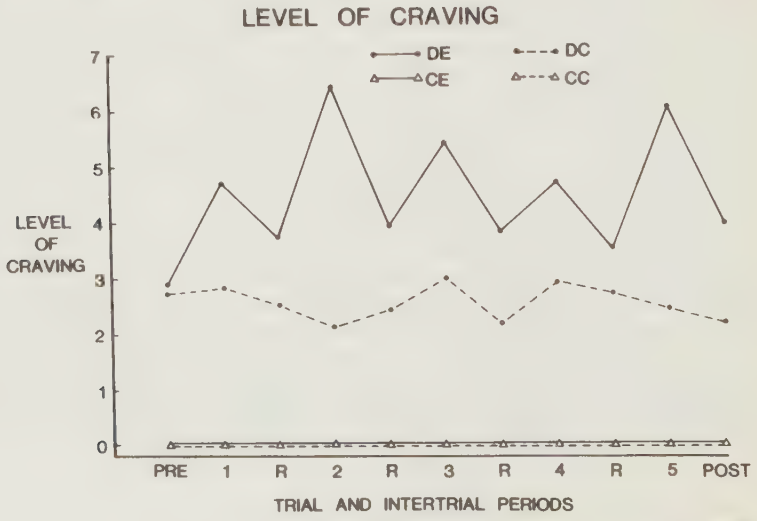
The actual VT material was presented in five two-minute trials, with one-minute intervals between trials. There were two VT's: an experimental VT showing various drug-related scenes including people preparing heroin and shooting-up, and a control VT showing neutral material. The two VT's were presented in a counterbalanced design on two successive days.

Upon completion of the second set of questionnaires, the experimenter talked with subjects, answering their questions and making observations on their physical appearance. Follow-up meetings were made to assure that there were no long-lasting effects from the videotape.

RESULTS

Figure 1 presents mean levels of craving during trial periods and intertrial rest periods (indicated with an 'R') for control and drug groups. The data points were derived by choosing the level that was observed at the end of each interval. Control subjects, without exception, set their dial at "0" during the entire experiment. Looking at the mean baseline or "pre" data for the drug group it can be seen that the level of craving was basically the same at the start of the two videotapes, and that this level was maintained throughout the control stimulus presentation, actually dropping slightly over the session. On the other hand, during the experimental videotape, craving level increased during each of the trial periods as compared to the immediately prior intertrial interval; in fact, craving levels were higher during each trial than during any rest period. Mann-Whitney comparisons indicated significant differences between the two videotapes for the drug subjects for all but the fourth trial period ($p<0.05$).

Figure 1. Mean level of craving for each of the four conditions:*

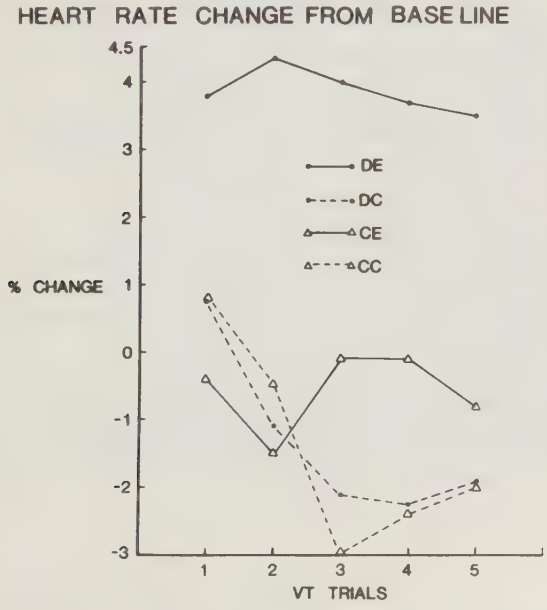


* DE -- Drug group, experimental VT
  DC -- Drug group, control VT
  CE -- Control group, experimental VT
  CC -- Control group, control VT

Levels of anxiety, depression and hostility as measured on the MAACL showed no significant change as a consequence of viewing either videotape, unlike results from the previous study (Sideroff and Jarvik, in press). It should be noted, however, that prevideotape scores were highly variable from subject to subject as well as within subjects from one session to the next. Similarly, the POMS yielded no significant changes with high inter- and intra- subject variability. On the other hand, a double blind examination of the "Draw-a-Person" test by an outside judge with experience in this projective technique, showed some interesting results. The judge was given the drawings in pairs: before and after videotape, in a random sequence for the four conditions, and asked to select those pairs which showed an increase in confusion, anxiety, disorientation or decompensation. She picked out a total of 15, of which eight were from the DE group, two were from the CE group, two were from the DC group, and three were from the CC group. In addition, the judge pointed out that in several other cases (all by the drug group) the first drawing was so regressed (e.g. "stick" figures) that it was impossible to detect an increase in the factors we were looking for. Thus, while the results were not statistically significant, they do indicate a trend toward the DE group effect.

Figure 2 presents percent heart rate changes from baseline for the four experimental conditions over the five trial periods.

Figure 2. Percent heart rate change from baseline.



It should be noted that there were no significant differences in heart rate baseline for the four conditions. From the figure, one can see a consistent increase in heart rate during the DE condition, with all other groups showing primarily a heart rate decrease. Analysis of variance of scores summed across trials showed significant differences between the DE and DC conditions ($p<.001$) and between the DE and CE conditions ($p<.05$). Of the 12 drug subjects, eight showed heart rate increases, while the other four were either flat or a deceleration during the experimental videotape.

Respiration data showed the same pattern, i.e., eight experimental subjects showing increases and four showing basically a decrease. Significant differences between groups, however, were not found. This, as with our earlier study, appears to be due to extreme variability. Mean respiration changes as a percent change from baseline were: 9.5 for DE; 5.8 for DC; -0.9 for CE; and -2.7 for CC.

Looking at the GSR we found the DE group had a significant increase in number of responses to the VT, with no comparable change in the other groups. Pre-VT response levels did not differ between groups.

Skin temperature yielded variable results. To begin with, due to problems with our equipment during the running of some of our subjects we have skin temperature data for only eight of the experimental subjects and six control subjects. What we found was that four of the subjects, during the DE condition demonstrated systematic decreases in temperature of between 0.3 and 1.3 degrees centigrade on at least three of the five trials. The only other change noted was an increase in temperature during some trials for the CC condition.

DISCUSSION

In this study we have attempted to obtain conditioned psychological and physiological responses in drug addicts to stimuli associated with their drug-taking behavior. In doing so we wanted to replicate our earlier research and to extend the findings in order to better characterize these responses. Furthermore, we believe that the elicitation of the conditioned responses in the laboratory setting might be a first step in determining a patient's "Readdiction Liability".

The data clearly demonstrated that the addicts differentially responded to the drug-related stimuli, and that the responses were unique to the addicts when compared with an appropriate control group. These differences were notable in the craving responses, where a sharp elevation was found during each drug-related stimulus trial. In addition, heart rate and GSR showed increases consistent with the expectation of a conditioned withdrawal response. The other physiological measures, respiration and skin temperature, while not significantly different from controls, were still in the expected direction of change. The data is also consistent with the results of O'Brien et al. (1976), where responses were conditioned within the laboratory.

It was difficult to analyze some of the data of the present study. To begin with, not all drug addict subjects demonstrated a responsivity to the experimental videotape, and tended to deny any negative feelings (as indicated in the questionnaire responses) both before and after its presentation. In a sense we seemed to have a dichotomy in the experimental population that we tested. On the one hand were the drug addicts who seriously were interested in becoming drug free, or at least were very concerned with their drug problem. These subjects consistently were affected by the videotape as indicated in our psychological and physiological data. The second group of drug addicts we tested were very "cool". Nothing was going to affect them, their drug habit really wasn't a problem, and they were participating in the experiment because it was good money. These subjects, as measured by the MAACL and POMS tended to deny their feelings, responded to a minimum number of feeling states, and, in general, appeared to be unaffected by the experimental procedure.

To at least partially deal with this problem we explored the use of a projective test in which the subjects were not as facile in hiding their emotions. This test, "Draw-a-Person", was at least partly successful in demonstrating increases in anxiety, confusion, as well as regressive tendencies in the drug addicts to the experimental videotape. As mentioned in the results section, some subjects were difficult to detect in this manner since their pretest pictures demonstrated what might be expected in the posttest picture. This, as well as other responses, might be a function of their status in the detoxification program. Since most of the subjects were just finishing detoxification from opiates, it might be expected that their baseline levels would be somewhat erratic.

The physiological data also showed a dichotomy mentioned above, with some experimental subjects demonstrating clear responses, particularly heart rate and GSR, and to a lesser extent in skin temperature and respiration. The fact that some subjects show consistent conditioned responses while others do not respond at all has important implications for a test of "Readdiction Liability". It would be important to be able to discern beforehand if a low response level is an indication that that person is less likely to develop conditioned withdrawal in his home environment, or if he simply is denying during the test presentation. In our current research procedure we are preceding the videotape presentation with questionnaires that we hope will discriminate between these two populations (such as the Lykken Activity Preference Questionnaire). Our readdiction liability test procedure, therefore, might only be applicable to the subpopulation that responds in some way to the conditioned stimuli, or the subpopulation that does not deny their problem.

The variability in some of our data points to the possibility that the detoxifying subjects were still experiencing abstinence effects that at times masked the effects of the drug-related stimuli. Thus it would be important in future studies to employ subjects not encumbered by, or at least minimally affected by, protracted abstinence.

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Unreinforced Self-Injections: Effects on Rituals and Outcome in Heroin Addicts

O'Brien, C. P.; Greenstein, R.; Ternes, J.; McLellan, A. T.; Grabowski, J.

The work of Abraham Wikler (1973, 1974) over the past three decades has focused attention on the conditioning aspects of the addiction process, and provided a theoretical foundation for some of the clinical approaches to opiate addiction, particularly the use of narcotic antagonists (Wikler 1974). While a patient is receiving an antagonist such as naltrexone, he can be exposed to stimuli which provoke opiate use and even use opiates with little or no reinforcement. However, urinalysis results and patients' self-reports (Kleber et al. 1974) indicate that most patients who are maintained on narcotic antagonists rarely test naltrexone by injecting heroin. The patients report that once they are convinced that opiate effects will be blocked by the antagonists, they do not wish to waste their money by using heroin.

While a few "test" injections are generally enough to convince the maintained client that the naltrexone will block primary reinforcement of the narcotic, these "test" trials are usually not sufficient to extinguish the associated drug-seeking and ritual injection behavior which have been shown to elicit drug-craving and even physical withdrawal. (O'Brien et al. 1975, 1977). Thus, when the naltrexone client terminates his antagonist therapy, he is once again susceptible to conditioning aspects of his environment which may promote readdiction. Studies by Meyer and his colleagues (1976) and our own group (Greenstein et al. 1976) confirm this impression, indicating that while heroin injection was quite low among active naltrexone patients (even when heroin was readily available at minimal cost), readdiction may occur in many clients following termination of naltrexone maintenance.

We have postulated (O'Brien, et al. 1975; O'Brien and Greenstein, 1976) that the effectiveness of naltrexone treatment could be enhanced and prolonged in combination with a supplemental regimen of behavioral extinction trials designed to reduce the conditioned effects of pre-injection drug rituals and self-injection behavior. In the present study, former addicts maintained on naltrexone were given opiate (hydromorphone) or saline to self-inject on a regularly prescribed basis in the laboratory. This paper compares

the six-month follow-up status of clients who received extinction trials, with those remaining naltrexone patients who did not participate in the procedure.

METHOD

Subjects

Subjects were 94 male veterans admitted to outpatient naltrexone treatment at the Drug Dependence Treatment Service of the Philadelphia Veterans Administration Medical Center. All subjects had been determined to be physically dependent on heroin or other opiates at the time of admission to treatment and all were then detoxified and stabilized on naltrexone (350 mg. per week), in a standard manner. A full description of this program has been provided elsewhere (Greenstein, et al. 1976; O'Brien, et al. 1978).

After discharge to outpatient status, twenty-one patients volunteered to perform self-injections in the laboratory according to experimental schedule. Patients were randomly assigned to one of three conditions. The Massed Trials Hydromorphone (Dilaudid) group (n=6) injected 2 mg hydromorphone at a frequency of four trials per day. The Spaced Trials Hydromorphone group (n=6) injected 2 mg hydromorphone at a frequency of three trials per week. The Spaced Trials Saline group (n=9) injected saline on a schedule identical to that of the Space Trials Hydromorphone group. Subjects in the Spaced Trials groups were run under double-blind conditions. Seventy-three additional patients receiving naltrexone but no behavioral treatment served as a "No Extinction" (NO EXT) comparison group.

General Extinction Procedure

Experimental sessions took place in a subject chamber equipped with audio speakers, a chair, table, syringe switch box, drug paraphernalia box (containing syringe, water, cotton, cooker, matches, bags of lactose, and belt), ash tray, sterile prepared syringe containing hydromorphone or saline, two TV cameras, a video pupillometer, thermistor, and TV monitor. Laboratory equipment included a Grass Polygraph, two video tape recorders, monitor, cassette player, switch for syringe box, videotape and cassette with music and instructions.

Skin temperature was recorded continuously throughout each session, and two-minute sessions of continuous pupil measurements were taken by video pupillometer periodically. Each trial was videotaped for subsequent ethological analysis in which independent observers scored the frequency of a number of behavioral responses. Subjective measures were verbal self-reports (VSR) to various tape-recorded questions which were presented five times during each session. Experimental sessions lasted about one hour depending on the length of the individuals' pre-injection ("cook-up") ritual and the ease with which each patient was able to self-inject.

After signing an informed consent, the patient entered the experimental chamber, a temperature sensor (thermistor) was taped to his finger, and the pupillometer head brace was adjusted. Baseline measures were recorded and the patient was then instructed to begin cooking-up. The patient cooked-up and prepared a syringe using the paraphernalia provided for him. The "drug" was powdered lactose packed in glassine bags to look like heroin. The patient typically would empty the contents of one or more bags into a cooker, add water, heat the solution to boiling, draw it into his "works," and then place the syringe into a black box on the table while waiting for the instruction to "shoot-up." The box contained an identically prepared syringe on a revolvable turntable. During the brief interval between "cook-up" and "shoot-up," the electrically operated mechanism silently rotated 180 degrees. This substitution procedure insured that the patient always injected with a sterile syringe. Subjects were informed that the syringe would be switched for the purpose of sterility and all willingly accepted the substitution. When the syringe box was activated and the sterile syringe became accessible, the patient was instructed to begin "shooting up." He then removed the sterile syringe from the box, tied his arm with the belt, and self-injected. Following "shoot-up" the patient sat quietly for another 15 minutes until the session ended. All subjects were eligible for the standard clinical follow-up procedure by an independent interviewer six months following treatment. An 84 percent contact rate was maintained for all patients, with no significant ($p > .10$) between-group difference.

Spaced Trials Procedure

Subjects in the Spaced Trials group attended sessions three times per week (usually Monday, Wednesday, and Friday) either 48 hours after a 100 mg. dose of naltrexone, or 72 hours after a 150 mg. dose. Patients received $2.50 per trial with payment at the end of each week. Patients were offered a $25 bonus if they completed 18 trials, however they were allowed to drop out of the study whenever they wished. Spaced Trials subjects were randomly assigned to either the hydromorphone or the saline group, and were tested under double-blind conditions throughout.

Massed Trials Procedure

Subjects in the Massed Trials group attended sessions on three consecutive days each week and were given four trials per day. The first syringe each day contained saline while the remaining three syringes contained hydromorphone. Naltrexone was administered approximately one-half hour prior to the start of the session each day, in order to eliminate the reinforcing effects of the accumulated hydromorphone. Patients received $50 upon completion of the twelfth trial and $25 for participating in a follow-up interview.

RESULTS

Admission Status

Subjects in each of the four groups were compared across nine admission status variables to determine the extent to which they differed at the outset of naltrexone treatment. Since no significant differences were found between the three extinction groups, they were combined into a single extinction (EXT) group (n=21) for subsequent comparisons with the NO EXT group (n=73). Chi-square comparisons ($p > .10$) show that groups were essentially equal in terms of admission status prior to the start of naltrexone treatment.

Within-Treatment Changes

Both subjective and physiological responses to the self-injections changed markedly over the course of trials. While the entire injection procedure (including pre- and post-injection rituals) was reported as mildly pleasant after the first few trials, subsequent trials were reported as being increasingly aversive. This change in affective responses replicates similar results reported by our group under similar conditions (O'Brien, 1975).

For the majority of subjects in all extinction groups, the pre-injection rituals of "cooking-up" and "tying-off" produced physiological signs of craving and withdrawal. While the early self-injections (either saline or hydromorphone) relieved the withdrawal and produced weak opioid effects, the later self-injections served to increase the withdrawal response. These changes in the physiological signs of craving are illustrated by the graphs in Figure 1 which plot one of these measures (skin temperature) over sessions 1 through 4 for a typical massed trials subject. The switch from pleasurable effects to withdrawal effects occurred regardless of whether saline or hydromorphone was self-injected.

The self-injection procedure grew increasingly aversive over the course of trials and this was especially pronounced in the Spaced Trials Saline group. Several patients became angry and refused to continue the injections despite cash inducements. While the Massed Trials Hydromorphone and the Spaced Trials Hydromorphone groups each completed an average of nine self-injections, the Spaced Trials Saline group averaged only five trials ($F < 1$, $p > .10$). The NO EXT group averaged 58 days of naltrexone treatment, while the Massed Trials Hydromorphone and Spaced Trials Hydromorphone averaged 53 and 56 days of treatment respectively. However, the Spaced Trials Saline group completed an average of only 31 days of treatment, significantly ($t=4.16$, $p < .05$) less than the other three groups.

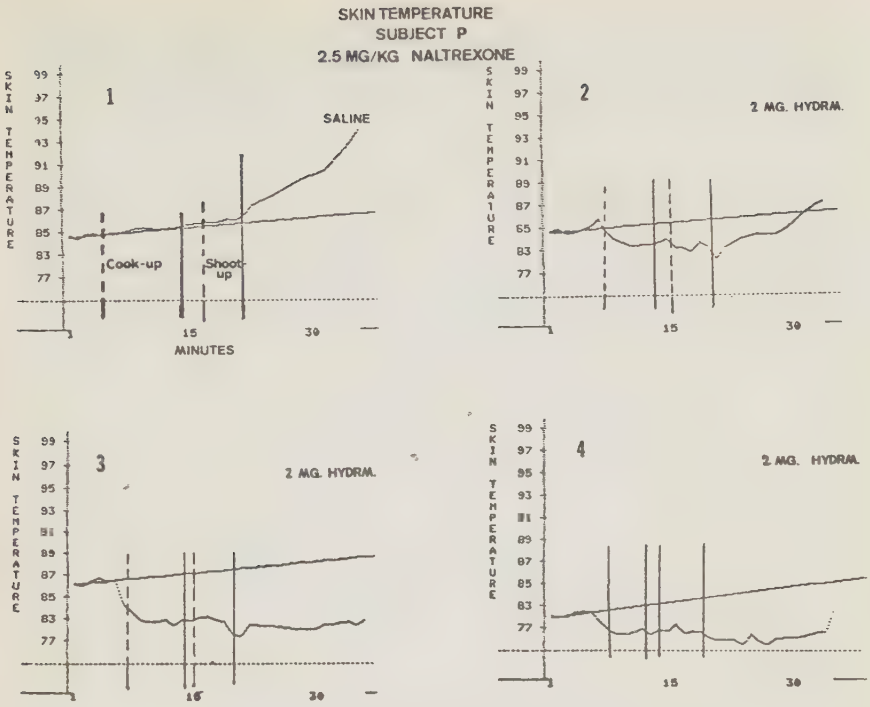

Figure 1: In trial 1, the pre-injection ritual and self-injection produced elevated skin temperature (an opiate effect associated with pleasure). However, in trials 2, 3, and 4 temperature became progressively lower and this was correlated with reports of opiate withdrawal feelings and increased drug-craving.

Post-Treatment Changes

The overall effectiveness of naltrexone treatment alone was examined through a comparison (chi-square) of nine performance criteria at admission and six months following treatment in the NO EXT group. Results indicated that there had been improvement in all nine criteria, and four of these were significant ($p < .05$), including drug use (especially heroin), illegal activity, and employment. As expected, comparisons of admission and follow-up performance criteria for the EXT group also showed similar improvement across all nine measures, signficantly so ($p < .05$) in five of them.

The clinical effectiveness of the extinction procedures was assessed by comparing the follow-up status of the four groups. Since previous analysis of the admission status and demographic variables had indicated no significant ($p > .10$) differences among the four groups at the outset of treatment, we felt at liberty to analyze outcome data directly. Ten performance criteria as well as three additional measures which were collected only at follow-up, were compared among the four groups. Results of these comparisons

indicated no significant ($p > .05$) differences among groups, although the extinction groups, particularly the Massed Trials Hydromorphone group, showed the best outcome in the majority of variables examined. There was reason to expect the lack of statistically significant differences among the four groups when compared on any single criterion, since we had few subjects, and the general improvement due to naltrexone alone was quite high. However, it was still possible that there were general improvement differences among the groups when compared across all measures. As a test of this possibility, four of the original performance criteria and the combined urinalysis results were summarized into five measures, and the groups were rank-ordered on the basis of their improvement since admission. These ratings, summarized in Table I,

TABLE I

GROUP IMPROVEMENT RANKINGS ON SIX-MONTH FOLLOW-UP MEASURES

(1=Best Outcome)

GROUP	% on DPA	% Unemployed	% Arrested	Positive Follow-up Urines	# Drugs Used
MASSED HM	1	1	2.5	1.5	1
SPACED DIL	2	2	2.5	1.5	2
NO-EXTINCTION	3	3	4	4	4
SPACED SAL	4	4	1	3	3

$X^2 = 29.4$ df 12, $p < .01$

demonstrate the differential effects of the extinction procedures after six months. As can be seen, subjects in the hydromorphone extinction groups (especially the massed trials group) showed the greatest general improvement while NO EXT subjects and the Spaced Trials Saline group showed the least ($X^2=29.4$ df 12, $p < .01$). No significant differences were detected between the two hydromorphone groups ($p > .12$) or between the Spaced Trials Saline and the NO EXT group ($p > .25$).

DISCUSSION

The results of this study suggest that naltrexone is an effective treatment plan for narcotic-dependent clients, particularly when it is combined with behavioral extinction procedures. The comparison of pre-treatment and six months post-treatment status in those clients who received naltrexone for at least two weeks, indicates clear improvement which appears to be directly related to the treatment modality. Furthermore, these improvements were manifest across the full range of outcome variables studied, including the important areas of drug use, crime, employment,

and psychological status (data not presented here). In addition to the general improvement in all groups treated with naltrexone, those subjects who received supplemental blocked self-injections of hydromorphone showed improvement above that shown in the NO EXT and the saline extinction groups.

The pre-injection rituals were effective in producing withdrawal as measured both by subjective reports and physiological changes. This withdrawal was partially relieved or even reversed by the first one to three injections, but subsequent self-injections only increased the signs and symptoms. These changes in the effects of self-injection were more rapid and more aversive for subjects receiving saline than for those who recieved hydromorphone. The difference may be partially explained by mild opiate effects caused by hydromorphone even in the presence of naltrexone.

Our results are also of interest because they are the first indication that changes in self-injection behavior during treatment may be associated with effects on clinical outcome at follow-up. Those who received saline improved less, and those who received massed trials actually did better than expected. Neither group turned out to be an optimal test of the extinction hypothesis because both had persistent conditioned withdrawal responses as a result of self-injections even in the final trials, indicating that extinction was not complete.

We cannot be sure whether the poorer outcome in the saline group was a cause or a result of their shorter treatment duration. We were struck by the aversiveness created by the saline injection procedure, and it may be that the frustration and anger associated with these trials had a negative clinical effect. Had we been able to retain these patients in treatment and to convince them to complete the full course of self-injections, the conditioned withdrawal responses may have diminished, producing a better clinical outcome.

These findings must be considered preliminary due to the small sample size and the fact that individuals in the extinction groups were self-selected. Still the data suggest that attempts to "extinguish" putative conditioned responses in opiate addicts can have either beneficial clinical effects or detrimental effects, depending on how these procedures are applied. We are now testing a more gradual extinction procedure which will be preceded by systematic desensitization of the pre-injection stimuli. It is our hope that this gradual procedure will lead to a more thorough extinction and ultimately a better clinical outcome.

ACKNOWLEDGEMENT

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Due to shortage of space, references are not presented here. They can be obtained from the senior author upon request.

AUTHORS - See author index.

Conditioned Drug Responses to Naturalistic Stimuli

Ternes, J. W.; O'Brien, C. P.; Grabowski, J.; Wellerstein, H.; Jordan-Hayes, J.

Research with both animals and humans has demonstrated that conditioned drug reactions can be produced in the laboratory when neutral stimuli are paired with narcotic drugs. Two different and apparently opposite types of conditioned responses have been identified. One, a positive affective reaction, mimics the agonistic effects of the drug US. Schuster and Woods (1968), for example, have shown in monkeys that a stimulus paired with injections of morphine acquired secondary reinforcing properties which were capable of maintaining an operant for drug infusion even after the subjects were completely withdrawn from morphine. Roffman, Reddy and Lal (1973) reported that a tonal stimulus could delay rectal temperature changes in addicted rats being withdrawn from morphine. The occurrence of conditioned drug-positive reactions in humans has also been reported. Levine (1974), for example, found that some addicts report pleasure from self-injection of inactive substances. O'Brien (1975) observed that positive affective and physiological changes occur in some drug addicts when stimuli previously associated with drug attainment or relief of withdrawal are present.

The second and more common type of conditioned drug response is a negative affective reaction which mimics the effect of an opiate antagonist. Wikler (1965) showed that environmental stimuli could evoke withdrawal reactions in rats previously withdrawn from opiates in the presence of those stimuli. Goldberg and Schuster (1969) found that monkeys could be conditioned to show withdrawal symptoms to stimuli associated with nalorphine (a narcotic antagonist) administration. Siegel (1976, 1977) argued that tolerance to morphine-induced analgesia and hypothermia is a Pavlovian conditioned compensatory response.

Clinical evidence for conditioned responses in human addicts was reported by Wikler (1948). He described the process as follows: when the drug-free "ex-addict" returns to the environment (the CS) in which he formerly used drugs (the US) he develops strong craving and autonomic changes (the CR) which are similar to the withdrawal state (the UR). Teasdale (1973) reported that slides

of drug-related scenes arouse anxiety in addicts. O'Brien et al. (1974, 1975) found that negative affective and physiological changes occurred both in drug-free former addicts and in patients maintained on methadone when they were presented with drug-related stimuli.

Recently Sideroff and Jarvik (1978) have also reported that heart rate changes can be elicited in addicts undergoing detoxification when they are allowed to view videotapes of drug administration procedures. While these results are suggestive of the naturally conditioned responses which we hypothesize, no systematic demonstration of such responses has been reported either in maintained addicts or in drug-free exaddicts.

Our group has had considerable experience eliciting both conditioned and unconditioned withdrawal reactions (O'Brien et al. 1975, 1977). Unconditioned withdrawal has been elicited by administering naloxone to patients in methadone maintenance. Generally the result observed is a standard withdrawal syndrome, including skin temperature decrease, pupillary dilatation, heart rate increase, respiration increase, and an elevation of the skin resistance response. We also have observed an increase in objective withdrawal signs, such as stomach cramps, nausea, yawning, lacrimation, sweating, and nasopharyngeal congestion. Finally, our patients' subjective reports indicate an increase in craving for drugs and in feelings of withdrawal.

Conditioned withdrawal (O'Brien et al. 1977) was produced in methadone maintenance patients by pairing neutral stimuli (sounds and odors) with a narcotic antagonist (naloxone). After 12 pairings we found that these CSs presented alone elicited withdrawal reactions. In addition we have found (Ternes and O'Brien, in preparation) that when drug-free patients blocked on naltrexone perform a cook-up ritual and then self-inject either saline or hydromorphone, the pattern of physiological, subjective and behavioral responses is similar to the standard withdrawal pattern. We have also observed this withdrawal pattern in response to drug preparation rituals and saline injections in both drug-free former addicts (not blocked on naltrexone) and in methadone maintenance patients.

We have now obtained further evidence of conditioned drug responses to naturalistic drug-related stimuli. We have tested the effects of the placebo (saline injections) and ineffective drug doses (e.g., hydromorphone challenge during naltrexone blockade), in addition to effects of rituals preceding drug administration ("cook-up"), videotapes of these procedures, slides of drug-related scenes, and drug objects ("works"). We have found that the most realistic and powerful drug CSs are embedded in the drug-preparation ritual and act of self-injection. In this paper we will primarily be concerned with the demonstration of conditioned withdrawal responses to slides, videotapes, and objects. Presented alone, these stimuli are not as powerful as drug rituals and placebo administrations; however, the demonstra-

tion of their effects, that is, their ability to evoke withdrawal-like responses, is an important step toward the development of a behavioral model of addiction.

METHOD

This experiment involved presenting naturalistic stimuli to three different groups of subjects: patients in methadone maintenance (MM), drug-free patients who had been detoxified for at least two weeks (DF) and normal controls who had never used heroin (CC). Stimuli were presented in six separate sessions. Three different stimulus modes were used: slides, videotapes, and objects. Two types of stimuli (neutral and drug) were presented in each modality. Data was also recorded during two baseline sessions in which no stimuli were presented.

Each session consisted of thirty minutes of baseline followed by ten minutes of stimulus presentation. Dependent measures included the autonomic variables of skin temperature, and heart rate (HR). Withdrawal was measured with the Weak Opiate Withdrawal (WOW) scale and mood was measured with the Profile of Mood Scale (POMS). Both POMS and WOW were administered before and after each session.

RESULTS

All physiological data were normalized by dividing each minute during the 10-minute stimulus period by the mean of the 10-minute baseline which preceded it. Analysis of variance (ANOVA) for each variable was performed on the transformed scores. The design was a 3 x 2 x 3 in each case.

Temperature

The effect of Groups was highly significant ($p < .005$) and indicated that temperature was generally lower in the MM and DF groups. The main effect for Type of stimulus was also highly significant ($p < .005$), as was that for Modality ($p < .001$). The Groups by Type interaction was also significant ($p < .025$). Figure 1 shows the groups' mean skin temperature scores plotted as a function of stimulus type. Appropriate two-group comparisons between neutral and drug stimuli have indicated that drug stimuli produced reliable decreases in skin temperature in both the MM and the DF groups but not in the CC group.

Heart rate

The main effect for Groups was highly significant ($p < .005$). The HR was higher in the MM and DF groups than in the CC group. The main effects for Type of stimulus and Modality were also significant ($p < .001$ and $p < .05$ respectively). Figure 2 shows the group mean HR plotted as a function of stimulus type. The Groups by Type interaction was also significant ($p < .05$). Appropriate two-group comparisons indicated that the drug stimuli produced reliably higher HR in the MM and DF groups relative to

the CC group. However, only the MM group's HR was significantly higher during drug stimulus presentations relative to neutral stimulus presentations.

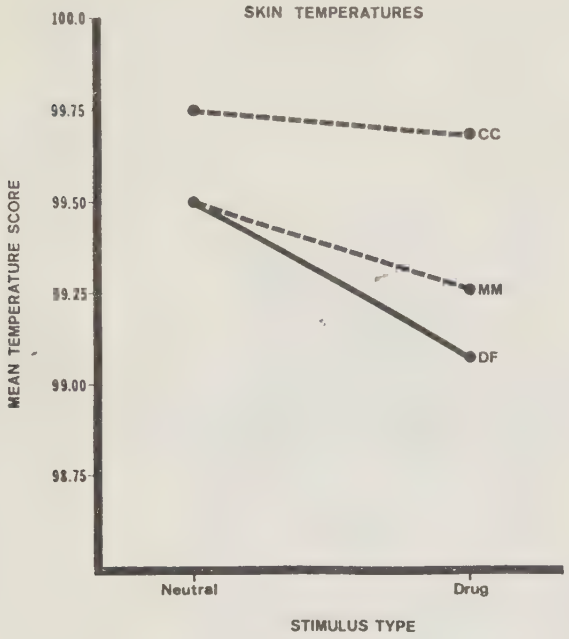

Figure 1: Group mean skin temperature scores

WOW Scale

This scale provided a measure of subjective withdrawal reactions. None of the changes in the pre- and postsession WOW scores were significant for any group. Although the MM and DF subjects did not report a high level of withdrawal, their scores tended to be higher after drug as opposed to neutral stimulus presentation, whereas the CC scores tended to be lower. This trend is reflected in Figure 3, which shows the sum of the rank order differences between neutral and drug postsession scores for the three groups.

POMS

We calculated scores for each of the Depression (D), Anger (A), Tension (T), Vigor (V), Fatigue (F), and Confusion (C) subscales of the POMS. For purposes of analysis, the POMS presession scores were subtracted from the postsession scores. No significant differences were found between pre- and postsessions for drug or neutral stimulus presentations for any of the three groups. However, some individuals in both the MM and DF groups did show large postsession changes in mood after the drug stimulus presentations.

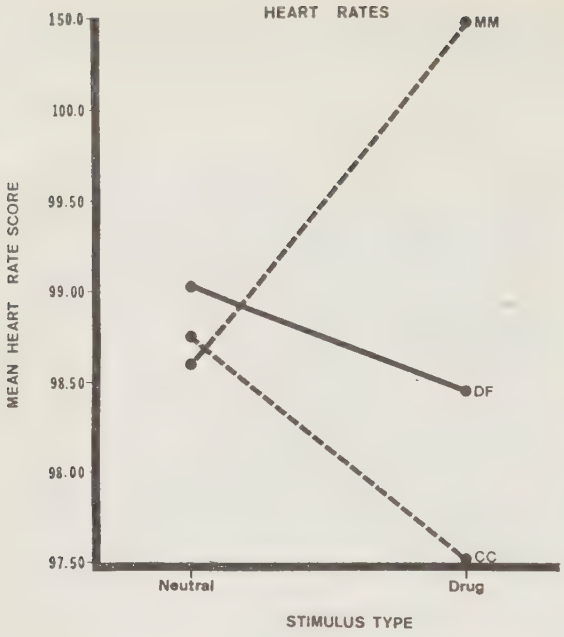

Figure 2: Group mean heart rate scores.

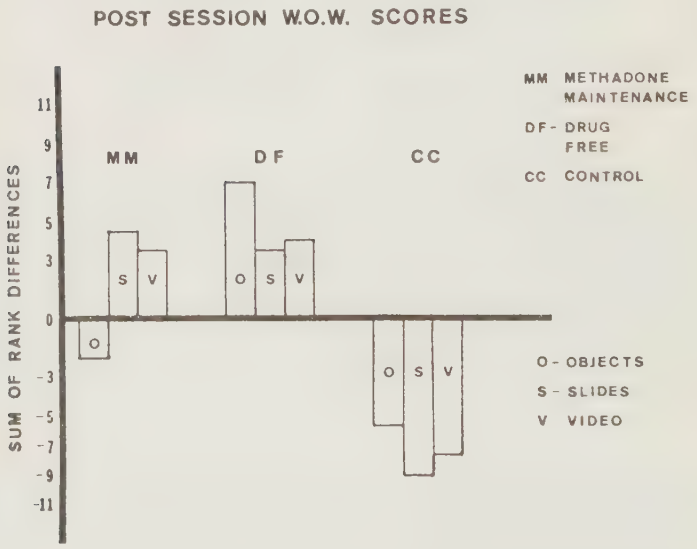

Figure 3: The sum of the rank order differences between neutral and drug post-session WOW scores for MM, DF and CC groups for each stimulus modality

An arousal score was derived from the T, V, F, and C subscales of the POMS. Figure 4 shows the mean pre-and postarousal scores for each group across the eight experimental sessions. Although

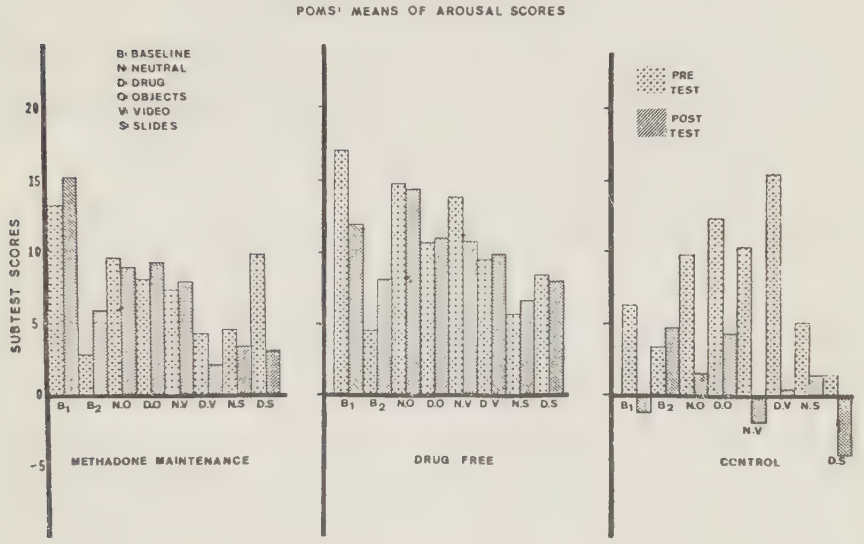

Figure 4: Mean pre-and postarousal scores for each group across the eight experimental sessions. The arousal score is derived by subtracting the sum of the F and C scores from the sum of the T and V scores.

there was no systematic effect of drug stimuli upon general arousal in any of the groups, the figure indicates that the CC group was consistently less aroused than the DF and MM groups after both drug and neutral stimulus presentation. It also indicates that physiological changes reported above are not due to general arousal, since the MM and DF groups were aroused on all sessions both before and after the stimuli were presented.

DISCUSSION

We have found (Ternes and O'Brien, in preparation) that when drug-free patients blocked on naltrexone perform a cook-up ritual and then self-inject either saline or hydromorphone, the resulting pattern of physiological, subjective and behavioral responses is similar to the standard withdrawal pattern. We have also observed this withdrawal-like pattern in responses to drug preparation rituals and saline injections in both drug-free former addicts (not blocked on naltrexone) and in methadone maintenance patients. We believe that the patterns of responses reported in the present

experiment are components of the naturally conditioned withdrawal response. However, because the CSs were presented in a novel context the CR was attenuated.

The amount of associative strength that a CS or any component of a CS complex has attained can be demonstrated empirically by presenting each component by itself (that is in the absence of the US). This procedure is known as Pavlovian extinction. In general, any CR is said to have both specific and general or supportive components. These components may be acquired at different rates and likewise may also have differential extinction rates. Stimulus-specific instrumental responses are usually acquired more rapidly and are more susceptible to extinction. A number of investigators have found that while the stimulus-specific response to a CS may extinguish rapidly, one or more of the supporting components of the CR may be highly resistant to extinction. These may be elicited even when there is no remaining overt evidence that the CS is effective. For example, a dog which no longer salivates to the sound of a bell may still experience tachycardia when the bell is rung although there is no overt motor behavior to indicate that the bell still has any associative strength.

Our data suggest that conditioned drug responses are complex combinations of subjective, behavioral, and physiological responses. Most accounts of conditioned drug reactions emphasize the subjective (drug craving) and instrumental (drug-seeking) response components of the CR. We recognize the primacy of these components, however, our definition of the nature of Pavlovian conditioned drug responses leads us to measure the general physiological components of these responses as well. We believe that these supportive components are highly resistant to extinction and persist long after the subjective and motor components have dropped out. Generally these supportive components represent a pattern of autonomic responses which partially mimic withdrawal and which may be elicited when naturalistic drug-related stimuli are presented. This pattern of supportive responses may in turn evoke the more stimulus-specific instrumental responses which initially led to redosing and eventually to readdiction.

ACKNOWLEDGEMENT

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Due to shortage of space, references are not presented here. They can be obtained from the senior author upon request.

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The Phase III Clinical Evaluation of LAAM: I. Comparative Epidemiology of Mortality in LAAM and Methadone

Thomas, D. B.; Whysner, J. A.; Newmann, M. C.

Since its development in the early 1950's, levo-alpha-acetylmethadol, or LAAM, a derivative of methadone, has been established as safe and efficacious for maintainence therapy of heroin addicts (Blaine and Renault, 1976). As LAAM is able to prevent and relieve opiate withdrawal symptoms for up to 72 hours, it need only be administered three times a week, thus freeing the patient from a daily round of clinic attendence and all of the implications of take-home doses.

The current Phase III study of LAAM is a large-scale cooperative trial, involving 86 clinics nationwide. This article reviews mortality patterns among LAAM patients in this study and compares the data with findings on methadone maintenance patients, taken from the DARP and CODAP data sets. The clinical implications of these findings, for the management of patients on LAAM, will also be discussed.

PATIENT POPULATION

Subjects are inducted into an open protocol, or randomized to LAAM or methadone. Both groups include men new to drug maintenance therapy and those previously stabilized on methadone.

Each patient is given a pretreatment evaluation consisting of a laboratory workup, physical exam, and medical and personal history. During the study, weekly urine screens, possible adverse reactions and a variety of other findings are reported. Upon completion of the trial (40 weeks or upon premature termination), each patient is again fully worked-up.

If a patient dies, the clinic follows a formal Autopsy Protocol. The protocol first directs the clinic to con-

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tact, and gain cooperation from local coroners, and then obtain a copy of the coroner's autopsy report. Also, clinics submit samples of blood, urine, and other tissues to Dr. Brian Finkle at the University of Utah, Salt Lake City, for analysis of LAAM and its metabolites. A broad screen for other drugs of abuse is also performed.

Thus, for the Phase III study, extensive and high-quality data are available, such that the specific cause of death can be determined for almost every case. Our only real problems have been obvious homicides; in these cases, coroners are under legal restriction, which limits their ability to release information.

CHARACTERISTICS OF THE SAMPLE

Intake for the Phase III LAAM study began in July 1976 and closed in April 1979. To date, 3,042 patients have been formally logged into the study for treatment on LAAM. Approximately 74% were crossed over from methadone, and 26% entered LAAM treatment directly. One protocol randomized patients to LAAM or methadone, and 524 patients received methadone. This last group of patients is too small for stable estimates of mortality rates, so only data on LAAM patients will be presented here.

To provide a comparative data base for LAAM vs. methadone as a maintenance drug, two sets of data on methadone maintenance patients will be used. The earliest of these is the DARP (Sells and Simpson, 1976) data on patients inducted from June 1, 1970 to May 31, 1973 and followed up to March 31, 1974. During year 1 of DARP, 24 agencies provided data; this increased to 36 and 52 in the next two years. The reporting clinics are fairly well distributed nationally, but the 11,529 methadone maintenance patients included are not a probability sample, and their representativeness to the national universe has not been established. The DARP study population was broken into annual cohorts, defined as anyone in treatment on June 1 of a given year or entering during the following 12-month period. An individual remaining in treatment could be counted again in subsequent cohorts, so that the DARP population is aging in terms of exposure to treatment to some unknown extent.

The CODAP data, collected directly by NIDA from clinics receiving federal funds, provide the other body of methadone maintenance data. CODAP receives client data on about 90% of the nation's clinics; again, it is not a strict national sample, but its coverage should ensure representativeness. Data from a cohort of methadone maintenance patients inducted between July 1, 1976 and August 31, 1977 which provides a cohort of 23,111 patients will be used.

While both the DARP and CODAP data have been criticized for various reasons, by Glenn and Hartwell (1976) and Richman (1977), among others, they are sufficiently accurate to furnish useful estimates of the parameters to be described. They are also the only readily available data of a scale sufficiently large to compare with LAAM data. Both the CODAP and DARP data must be used, since neither has all the data required for a full comparison.

COMPARISON OF SAMPLES--BACKGROUND VARIABLES

The comparisons of distributions of available background variables across studies are summarized by P-values, relating to comparisons among groups, as shown in Table 1. Only age and race/ethnic status are available for the DARP cohort, so the rest of the variables only compare the Phase III LAAM and CODAP groups.

TABLE 1

Variable	P-Value
Age (DARP, CODAP, PH III)	$P > .05^1$
Race (DARP, CODAP, PH III)	$P < .01^2$
Marital Status (CODAP, PH III)	$P > .05^2$
Employment Status (CODAP, PH III)	$P < .05^2$
Educational Status (CODAP, PH III)	$P > .05^2$
Current Educational Status (CODAP, PH III)	$P > .05^2$
Length of Heroin Addiction (CODAP, PH III)	$P > .05^1$
Arrests Prior to Admission (CODAP, PH III)	$P < .005^2$

1) Continuous variable analyzed by the Analysis of Variance; 2) Catagorical variable analyzed by the Chi-square test.

Briefly, review of these distributions indicates that LAAM patients are slightly older, more often married, employed, more likely to have no arrests, tend to have shorter histories of addiction, and have somewhat more education than the DARP and CODAP patients. There are also fewer black and more white patients in the LAAM population than the methadone maintenance groups.

The previous analysis of DARP mortality (Watterson, et al., 1976) shows that mortality rates increase with age, but racial composition has no influence. Given the slight tendency for LAAM patients to have some social advantages over the other two cohorts, we might expect some reduction in mortality. However, the limited number of events upon which this analysis is based does not allow for partitioning of mortality rates for these background variables. Therefore, parameters to be estimated below must be considered with some caution and the results taken as preliminary pending the accumulation of further data.

RESULTS

Over the initial 40-week trial, 17 LAAM patients died. To compare experiences among studies, for each cohort, the number of patient days were summed and man-years of exposure computed. The death rate per 1,000 per man-year was then calculated, as shown in Table 2.

CODAP doesn't cite cause of death, but we can sub-divide these rates into the various categories used in DARP reporting. Overdose deaths are those secondary to direct drug effects, or reactions such as anaphylactic shock. Deaths secondary to the consequences of prolonged drug abuse, such as alcoholism, cirrhosis, or hepatitis are also included. Violent deaths encompass those due to traumatic events, such as homicide, suicide, auto accidents, etc. Medical deaths are those caused by a medical problem unrelated to drug abuse. Unknown deaths are those for which the data available are insufficient to assign a cause.

Mortality experience in the three cohorts has been fairly similar. The LAAM Phase III trial has had the lowest mortality rate (13.35 per 1,000 man-years), followed closely by the DARP cohort (15 per 1,000 man-years); the CODAP data, however, show somewhat higher rates (20 per 1,000 man-years). Interpreting these data, several potential influencing factors must be balanced. The LAAM population is somewhat older, so we would expect some elevation of mortality. The apparent advantages of LAAM patients, in terms of social adjustment may tend to move these rates in the opposite direction. The continual aging of the DARP cohort might tend to lower estimated rates. As will be seen below, this factor has a strong influence upon the probability of mortality.

TABLE 2
COMPARATIVE MORTALITY OF MALE DRUG MAINTENANCE PATIENTS
(man-years per 1,000)

	LAAM	METHADONE	
	Phase III (1976-1979)	CODAP (1976-1977)	DARP (1970-1973)
DEATH CATEGORY	(n = 3,042)	(n = 23,111)	(n = 11,529)
Overall Mortality	13.35	20.28	15
Overdose Deaths	5.50		4.55
Violent Deaths	5.50		6.24
Medical	1.57		3.46
Unknown	.78		.75

The breakdown of deaths in treatment by cause, as shown in the rest of the table (for the Phase III LAAM and DARP data only) is quite similar for both studies, given the

limited number of events which constitute the basis for these calculations in either study. These distributions by cause of mortality are graphically displayed in Figure 1, which reflects the excess of "medical" deaths in the DARP sample and more overdose-related deaths among the LAAM patients. As shown at the bottom of this figure, the distributions do not differ statistically from each other (by the chi-square test).

Reviewing the temporal distribution of deaths over the 40 weeks of the Phase III LAAM trial (Figure 2), there is a notable tendency for deaths due to all causes to occur soon after induction. Comparable data is not available for DARP patients, but is available for our CODAP cohort though it is only available aggregated for all causes. These data were used to calculate the probability of death for each two-week interval across the 40 weeks as shown in Figure 3. As with the LAAM data there is a striking tendency for mortality to be more frequent soon after induction.

This pattern may occur as a legacy of patients' previous drug abuse history and life-style. Also, patients at the highest risk of dying probably terminate early from treatment so that there is a lowering of aggregate risk of mortality over time. It is evident from these data reviewed here that the length of participation in a maintenance program has a strong effect upon the probability of dying. This implies that comparative analyses of mortality would do well to standardize this parameter in order to avoid misleading conclusions.

DISCUSSION

Since five of the overdose deaths occurred in the first week of therapy, very close observation, on a daily basis, seems indicated when a patient is beginning treatment with LAAM. In addition, strong psychological support and repeated admonition against the use of alcohol and other drugs, especially diazepam, should be prominent aspects of early LAAM therapy. However, two of these early deaths were due to a dosage of LAAM administered in amounts greater than the protocol allowed in conjunction with evidence of use of other drugs. Thus, three patients were treated properly in the early-death group. Methadone maintenance patients, as well as street patients, have probably developed a keen sense of just how much alcohol or tranquilizer they can tolerate while taking heroin or methadone. LAAM, however, has a slow onset and prolonged time-course of action, due to active metabolites; this drug therefore may make established patterns of ethanol and tranquilizer use obsolete, and occasionally lethal. Time and experience are required for the individual to learn how to accommodate himself

to this drug. However, the distribution of mortality among methadone patients reported to CODAP suggests that these admonitions might well be applied generally. Metabolic findings on these drug deaths and possible drug interactions will be reviewed in a future paper.

In conclusion, two essential points can be made:
1. Mortality experience in the LAAM Phase III trial follows closely the experience of methadone maintenance though these data should be considered preliminary.
2. Generally, the influence of time in treatment on the probability of mortality is strong enough to warrant avoiding comparisons between mortality rates where this parameter is not controlled.

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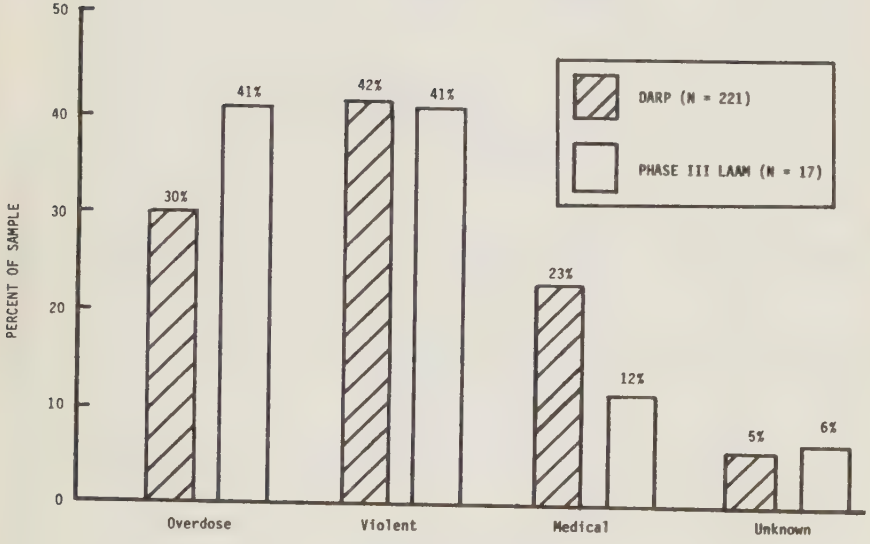
FIGURE 1

DISTRIBUTIONS OF TYPE OF DEATH:
DARP AND PHASE III LAAM STUDIES



$X^2 = 5.28$, df = 3, $p > .05$

FIGURE 2

TYPE OF DEATH AND DURATION IN THE STUDY:
PHASE III

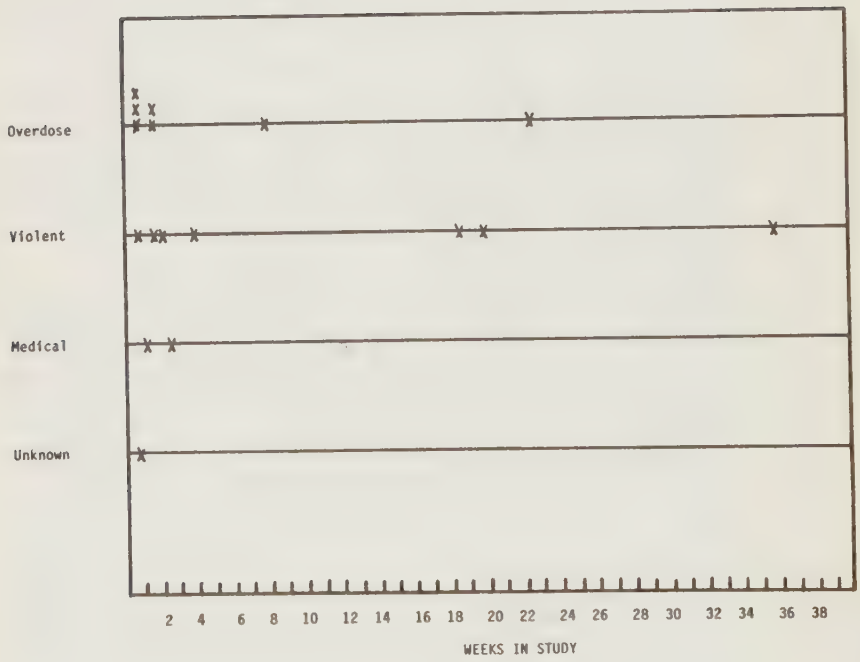


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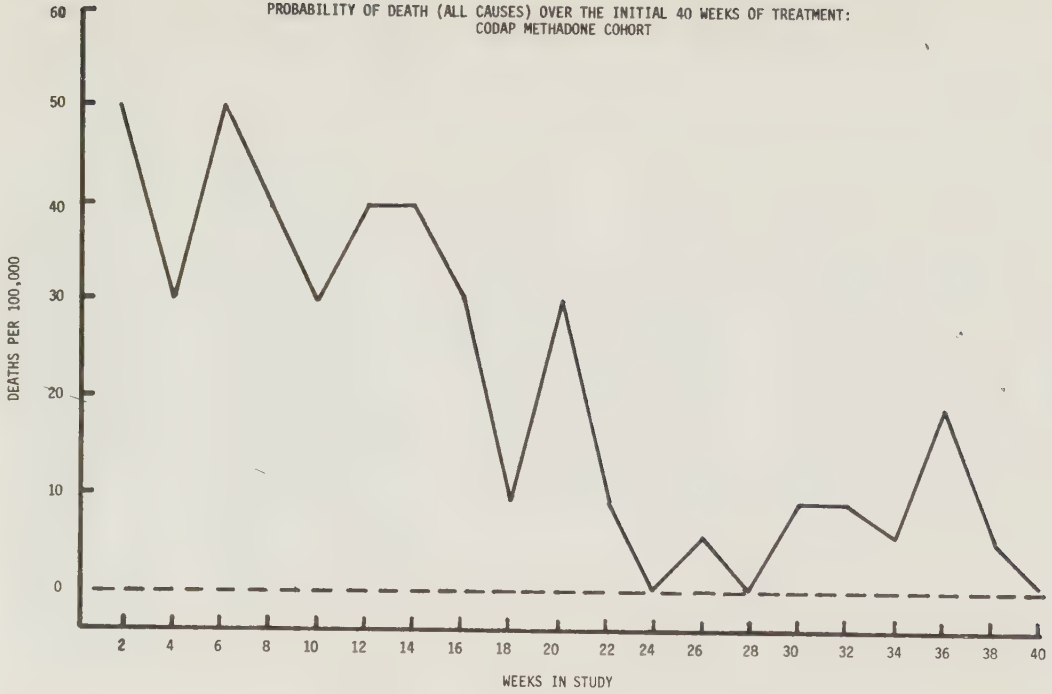
FIGURE 3

PROBABILITY OF DEATH (ALL CAUSES) OVER THE INITIAL 40 WEEKS OF TREATMENT:
CODAP METHADONE COHORT



Naltrexone, 6β-Naltrexol and 2-Hydroxy-3-Methoxy-6β-Naltrexol Plasma Levels in Schizophrenic Patients After Large Oral Doses of Naltrexone

Verebey, K.; Mulé, S. J.

ABSTRACT

From 100 to 800 mg daily naltrexone doses were given to six schizophrenic patients. The plasma levels of naltrexone, its major metabolite 6β-naltrexol (β-OL) and its minor metabolite 2-hydroxy-3-methoxy-6β-naltrexol (HMN) increased to very high levels without therapeutic improvement, toxicity or any other undesirable side effects. Two weeks after the discontinuation of the 800 mg naltrexone dose the plasma was free of naltrexone, 6β-naltrexol and HMN; indicating a rapid and efficient elimination of the drug from the body. The proposed role of naltrexone is opiate receptor blockade in narcotic post addicts to prevent readdiction to heroin. The effective heroin blocking dose for a 72-hour period is 100 mg of naltrexone. Even when naltrexone was used at considerably higher doses, as in this study, no undesirable side effects were noted; indicating a high margin of safety.

INTRODUCTION

Naltrexone, a reasonably pure narcotic antagonist, has been tested in man principally for the blockade of heroin-related euphoria in narcotic post addicts (Martin et al., 1973). Naltrexone may be effective in blocking the addiction-abstinence cycle by preventing re-addiction to heroin (Goldstein, 1976). In previous studies the naltrexone doses given to narcotic post addicts varied between 20 and 200 mg per day (Resnick et al., 1974). The effectiveness and safety of 100 mg daily oral doses of naltrexone was evaluated after acute and chronic administration. Naltrexone provided nearly 100% blockade of heroin-related symptoms for 48 hours and about 50% blockade at 72 hours. Other findings indicated no undesirable side effects; the drug was biotransformed to less active metabolites, 6β-naltrexol and HMN, which were excreted mainly into the urine (Verebey et al., 1976b).

The recent discoveries of the opiate receptor and the identification of the endogenous ligands (endorphins) in the brain provided therapeutic rationale for the use of opiate agonists as well as opiate antagonists in psychiatric patients (Verebey et al., 1978). The experiments utilizing an antagonist such as naloxone, N-allyl

congener of naltrexone, in chronic schizophrenic patients were found to be effective in eliminating auditory hallucination in some patients (Gunne et al., 1977), while attempted replications in similar studies were therapeutically unsuccessful (Volavka et al., 1977, Davis et al., 1977 and Janowsky et al. 1977). Since the oral effectiveness and longer time action of naltrexone seemed an advantage in chronic therapy, it was also evaluated for its possible effectiveness in schizophrenic patients, however, mostly without benefit (Mielka and Gallant, 1977 and Simpson et al., 1977).

In this report we present data on the plasma level of naltrexone, 6β-naltrexol and HMN in schizophrenic patients who received up to 800 mg naltrexone daily (Simpson et al., 1977). We also present a variation of the previously published method (Verebey et al., 1976a) that allows quantitative measurement of naltrexone and HMN and a separate extraction for 6β-naltrexol and HMN in plasma.

Materials and Methods

Subjects

Six chronic schizophrenic patients participated in the study. The age of the subjects ranged between 32 and 54 y.(average 44.2y). The length of hospitalization was 2 to 29 y. (average 13.3y).

Drug Administration

Naltrexone in 50 mg tablet form and naltrexone placebo tablets were provided by Endo Laboratories (Garden City, New York 11530).

The patients were tapered from their psychotropic medications to no medication, using minor tranquilizers such as diazepam when needed. During the first week placebo capsules were given BID at 8am and 4pm. During the 2nd week 100 mg naltrexone was given (50 mg BID); 3rd week 200 mg (100 mg BID); 4th week 300 mg (150 mg BID); the 5th, 6th and 7th week 400 mg (200 mg BID); 8th week 600 mg (300 mg BID) and the 9th week 800 mg (400 mg BID). Two weeks of placebo administration followed after which the subjects received the same medication as prior to the study.

Sample Collection

Blood samples were drawn after the patients received at least 3-4 days of the designated doses and the time of the day was just before the administration of the next morning dose. Thus the samples represent a time 24 hours after the 1st and 16 hours after the 2nd daily dose of naltrexone. The samples were heparinized and the plasma separated from the cells by centrifugation and frozen until analysis. Blank samples were taken before naltrexone therapy began and samples were taken two weeks after the conclusion of drug administration.

Method of Analysis

The procedure for the analysis of naltrexone, 6β-naltrexol and HMN in plasma was based on a previously reported method (Verebey et al., 1976a). In brief, following multiple organic-aqueous extractions of the drug, metabolite and internal standard, the puri-

fied bases were derivatized with pentafluoropropionic anhydride to form electrophores for electron-capture detection by gas-liquid chromatography. Naltrexone, 6β-naltrexol and HMN standards at various concentrations with the internal standard (nalorphine) provided standard curves for the quantitation of unknown samples. However, modifications were necessary for the determination of HMN in the presence of 6β-naltrexol. The problem of quantitation occurred because the HMN and 6β-naltrexol pentofluro derivatives were not separable by gas liquid chromatography. This problem was solved by differentially extracting HMN without 6β-naltrexol. This was accomplished by using a non-polar solvent, benzene, for the first and last extractions at pH 7.5, buffering with 0.2M tris-maleate. For the determination of 6β-naltrexol and HMN combined, the original method was used utilizing chloroform as the extracting solvent at pH 9.8. Nalorphine was used as the internal standard; using 12.5 ng for the chloroform procedure and 25 ng for the benzene procedure. The retention time of nalorphine is longer than 6β-naltrexol, HMN and naltrexone thus emerging at a locus on the chromatogram which is free from interfering plasma peaks. In order to facilitate reproducability, the column was conditioned prior to injection of the samples with 40 μl of Sylil-8 solution (Pierce Chemical Co., Rockford, Illinois 61105); this step minimizes the on column breakdown of the electrophore-drug complexes.

Results and Discussion

The results of the psychiatric evaluation of this study were reported in an earlier communication (Simpson et al., 1977). Briefly, the findings were that no therapeutic improvement was achieved at any dose level in the six chronic schizophrenic patients of whom three had auditory hallucination. Although the naltrexone doses were increased substantially no deterioration in the condition of any of the patients or complaints of side effects were noted.

Figure 1 shows the dosage schedule on the abscissa and the plasma levels of naltrexone, HMN and 6β-naltrexol on the ordinate. The levels of both drug and metabolites increased with increasing doses of naltrexone. The average 24-hr plasma levels of naltrexone in six subjects following 100 mg daily doses was 1.92 ± 1.0 ng/ml, which was lower than found in our earlier study (Verebey, et al., 1976) using the same dose (2.98 ng/ml). Higher rate of naltrexone biotransformation reflected by the lower than expected naltrexone plasma levels may have resulted from the chronic administration of large doses of phenothiazines in these patients causing induction of the drug metabolizing enzymes. The level of 6β-naltrexol of 40 ± 11 ng/ml was nearly twice that of the earlier data (24.2 ng/ml) in four narcotic post addicts (Verebey et al., 1976b). Since 6β-naltrexol excretion was shown to be an active secretory process (Verebey et al., 1976b), it is possible that the schizophrenic patients may have had problems with active renal clearance, resulting in the higher than expected 6β-naltrexol plasma levels. The highest 24 hour plasma levels of naltrexone, HMN and 6β-naltrexol at 800 mg daily doses were 9.2 ± 3.4 ng/ml, 123 ± 14 ng/ml and

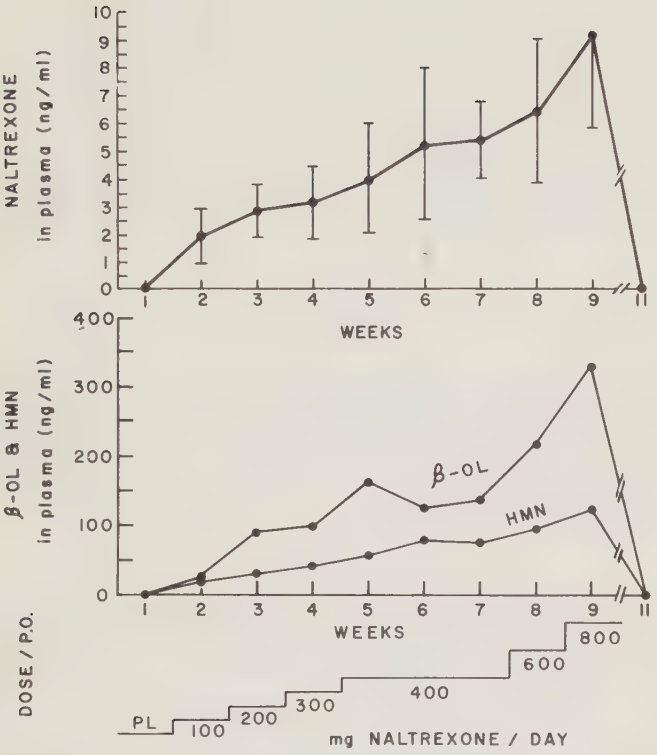


Figure 1

Naltrexone, 6β-naltrexol and HMN plasma levels determined in plasma obtained just prior to each daily dose of naltrexone. The incremental weekly doses are presented at the bottom of the figure. Each point on the curve represents the mean of n=6 at 0-6th week; n=5 at 7th week and n=4 at 8th and 9th week. The two patients who did not complete the study were dropped for medical reasons not related to naltrexone therapy. (see Simpson et al., 1977).

331 ± 35 ng/ml, respectively. These high drug and metabolite levels indicate good absorption and systemic distribution of the large doses of naltrexone with lack of toxicity or complaint of any undesirable side effects by the patients in this study.

In post heroin addicts optimal heroin blockade was accomplished at 100 mg daily doses of naltrexone (Verebey et al., 1976b and Volavka et al., 1976), representing 1/8th of the highest doses used in this study. Two weeks after the use of 800 mg daily naltrexone the levels of naltrexone, HMN and 6β-naltrexol were undetectable in the plasma, indicating that the drug is well cleared from the body. These results provide evidence for the large margin of safety of naltrexone, observed at significantly higher doses than the ones suggested for narcotic antagonist therapy.

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Heroin and Naltrexone Effects on Pituitary-Gonadal Hormones in Man: Tolerance and Supersensitivity

Mendelson, J. H.; Ellingboe, J.; Kuehnle, J.; Mello, N. K.

INTRODUCTION

A number of clinical studies have attempted to explore the relationship between opiate use and sex hormone secretion. Azizi found a significant diminution in plasma testosterone in 8 of 16 active heroin users compared to a group of normal controls (Azizi 1973). Cicero and co-workers (1975) found that long-term methadone administration produced a decrement in function of secondary sex organs in adult male heroin addicts. A decreased level of plasma testosterone was associated with these secondary sex organ derangements. More recently, we measured plasma testosterone in narcotic addicts, given known doses of heroin at fixed time intervals and found a significant dose-related depression of plasma testosterone levels (Mendelson et al. 1975a, Mirin et al. 1976). Testosterone suppression has also been observed in street addicts with a recent history of heavy heroin use and in patients on high dose (80 to 150 mg) methadone maintenance (Mendelson, Mendelson and Patch 1975).

The purpose of this study was to determine if tolerance develops to heroin-induced suppression of testosterone and luteinizing hormone in human opiate dependent males. A second purpose of this study was to ascertain if naltrexone administration to heroin users who were drug-free produced any changes in plasma levels of pituitary-gonadal hormones as a function of duration of opiate abstinence. Finally, these studies were carried out to assess tolerance and supersensitivity of prolactin secretory activity associated with heroin self-administration and naltrexone use during opiate abstinence.

METHODS

Six adult male heroin addicts provided informed consent for their participation in these studies. All six subjects (ages 23 to 28) were in good health as determined by appropriate clinical and laboratory examinations. All of the subjects had previously been unsuccessful in maintaining heroin abstinence following a variety

of behavioral, social and pharmacological intervention programs. The major motivation for subjects volunteering for this study was their desire to determine if naltrexone blockade would be efficacious in suppressing their heroin self-administration behavior.

The basic research paradigm involved a five-day drug-free baseline period, two days of acute single dose (10 mg I.V.) heroin self-administration with an intervening drug-free day, followed by 10 days of heroin self-administration under blocked (naltrexone) or unblocked conditions. Subjects who received naltrexone administered only one or two doses of heroin during the 10-day period of heroin availability. In contrast, subjects who received naltrexone placebo self-administered almost all available doses of heroin. Subjects who received naltrexone during the period of heroin availability (10 days) continued to receive naltrexone for an additional 16 days prior to their discharge. Subjects who received naltrexone placebo were detoxified with methadone for five days, were drug-free for the following seven days and were subsequently placed on naltrexone (50 mg/day) for four consecutive days prior to discharge.

Plasma samples were collected from an indwelling intravenous catheter connected to a portable non-thrombogenic pump following an acute intravenous injection of heroin (10 mg) on the 6th and 8th days of the study. Prior to these two acute doses of heroin, subjects were drug-free for at least 5 days. Plasma samples were also collected on experimental day 19 after a 10-day period of heroin self-administration when subjects could administer up to 10 mg of heroin every 6 hrs (total daily dose - 40 mg). Finally, plasma samples were collected on the 32nd day of the study when subjects were administered 50 mg of naltrexone orally.

Analysis of integrated plasma samples for testosterone were carried out by a double antibody radioimmunoassay modified from a procedure used for protein hormones by Niswander et al. and discussed in detail in previous publications (Mendelson et al. 1974, Mendelson et al. 1975b). Integrated plasma LH and prolactin concentrations were measured with a double antibody method similar to that described by Midgley (1966).

RESULTS

Table 1 presents mean integrated plasma testosterone and luteinizing hormone values for six subjects prior to and following acute heroin administration (10 mg I.V.) on Day 6 and Day 8 of the experimental period. On Day 6, heroin administration was preceded by five days of a drug-free baseline condition. Day 7 was also a drug-free day and on Day 8 the procedures carried out on Day 6 were repeated.

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Table 1

INTEGRATED TESTOSTERONE AND LH LEVELS FOR 6 SUBJECTS PRIOR TO AND FOLLOWING AN ACUTE DOSE (10 mg I.V.) OF HEROIN

	Testosterone ng/100 ml	LH ng/100 ml (LER 907)
	X ± S.E.	
Day 6		
Pre Heroin	1422 ± 247	44.5 ± 6.7
Post Heroin	1005 ± 168	33.2 ± 6.9
Day 8		
Pre Heroin	757 ± 68	41.8 ± 7.8
Post Heroin	669 ± 82	31.5 ± 5.2

Plasma testosterone levels were significantly higher on Day 6 when compared with Day 8. Heroin administration on both Days 6 and 8 was followed by a suppression of plasma testosterone levels. A 10 mg intravenous dose of heroin produced suppression of integrated LH levels on both Days 6 and 8, and the magnitude of suppression was almost identical for each day. Thus luteinizing hormone suppression following acute heroin self-administration appears to be a replicable phenomenon with respect to both magnitude and time course of LH changes.

The effects of acute naltrexone administration on plasma luteinizing hormone and testosterone levels for three subjects who self-administered heroin during 10 consecutive days and for one subject who was under naltrexone blockade and did not self-administer heroin are shown in figure 1. Plasma luteinizing hormone and testosterone levels were obtained on Day 32 of the study. Subjects 1, 2 and 3 (1HT-3, 1HT-2, 1HA-2) had received no opiates for seven days prior to Day 32. However, subject 4 had a significantly longer period of opiate abstinence of 21 days and in addition had received naltrexone (50 mg/day) during this period. Subjects 1, 2 and 3 showed a naltrexone-related increment in plasma luteinizing hormone levels. Subject 4 had low basal plasma luteinizing hormone levels prior to naltrexone administration and only a small increment following naltrexone administration. In addition, subject 4 had plasma testosterone levels which were significantly higher than either subjects 1, 2 or 3.

Table 2 presents integrated testosterone and luteinizing hormone levels for four subjects who self-administered heroin during the 10-day period of heroin availability. (These subjects received naltrexone placebo during the period of heroin availability.) Testosterone and luteinizing hormone levels following acute heroin administration, and as mentioned previously, luteinizing hormone

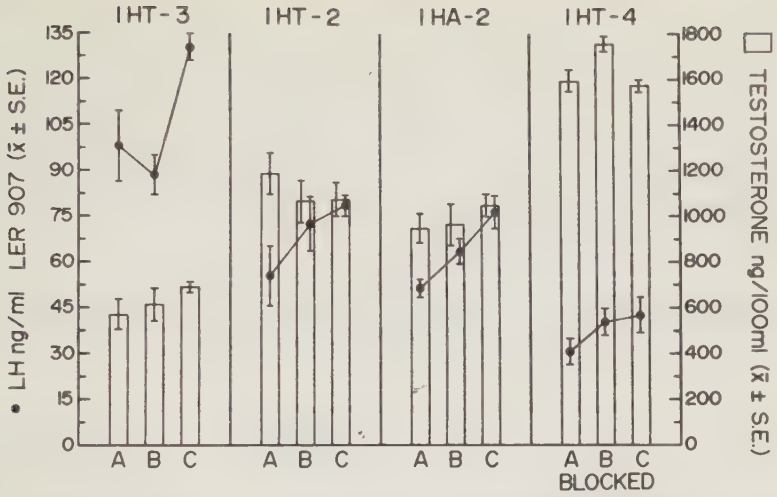

Figure 1: Effects of acute naltrexone administration (50 mg) on LH and testosterone levels in four individuals.
A= Pre naltrexone; B= 3 hrs post naltrexone;
C= 3-6½ hrs post naltrexone

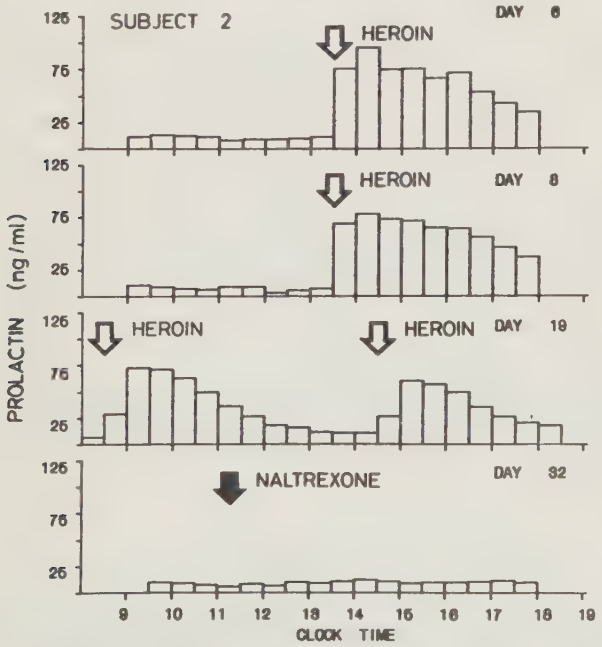

Figure 2: Integrated Plasma Prolactin Values for an adult male heroin addict. Day 6 and Day 8: 10 mg of heroin I.V. on an acute basis; Day 19: 2 doses (10 mg) of heroin I.V. on the last day of a 10-day heroin self-administration period; Day 32: naltrexone 50 mg P.O.

suppression appears to be a reliable and sensitive index of heroin effects.

The lowest integrated plasma testosterone levels were observed on Day 19 following 10 consecutive days of heroin self-administration. However, luteinizing hormone levels on Day 19 following heroin self-administration for 10 consecutive days were approximately the same as observed following acute heroin self-administration on Days 6 and 8.

Table 2

INTEGRATED TESTOSTERONE AND LH LEVELS FOR 4 SUBJECTS FOLLOWING ACUTE (Days 6 and 8) and CHRONIC (Day 19) DOSES OF HEROIN

	Testosterone ng/100 ml	LH ng/100 ml (LER 907)
	X ± S.E.	
Day 6		
Pre Heroin	1226 ± 176	51.3 ± 8.0
Post Heroin	967 ± 189	38.4 ± 9.0
Day 8		
Pre Heroin	780 ± 83	46.9 ± 7.7
Post Heroin	710 ± 91	34.6 ± 5.3
Day 19		
Post Heroin	615 ± 72	34.2 ± 5.9

Figure 2 shows heroin-induced increments of plasma prolactin levels for an adult male heroin addict. Acute administration of 10 mg of heroin on Days 6 and 8 produced a prompt and sustained increment in plasma prolactin levels. On Day 19, the last day of the 10-day heroin self-administration period, heroin administration was also associated with increments in prolactin levels. However, these increments remained sustained over a much shorter time course when compared with the acute dose reponses on Days 6 and 8. Naltrexone administration on Day 32 produced no changes in plasma prolactin levels.

DISCUSSION

The finding that acute heroin administration (on both Days 6 and 8) was followed by a suppression of plasma testosterone levels is consistent with data contained in experimental animal studies reported by others (Cicero et al. 1977) and previous research carried out with humans in our laboratory (Mirin et al. 1976). The observation that heroin-induced suppression of plasma testosterone and luteinizing hormone levels following a 10-day period of self-

administration is less than the degree of suppression following initial acute heroin dosage suggests that tolerance occurs with respect to heroin effects on both LH and testosterone levels.

Following cessation of heroin use, an increment in the basal level of luteinizing hormone levels was observed. At this time acute administration of naltrexone produced a further increase in plasma luteinizing hormone levels. These findings suggest that a "rebound" increment in plasma luteinizing hormone levels occurs following cessation of heroin use and that naltrexone accentuates this effect. These observations indicate that some degree of supersensitivity occurs at the hypothalamic and/or pituitary level regulating secretory activity of LH during opiate abstinence. Such supersensitivity is manifest even when subjects are not experiencing any overt opiate withdrawal signs or symptoms.

Although the lowest integrated plasma testosterone levels were observed following 10 consecutive days of heroin administration, luteinizing hormone levels were approximately the same as those observed following acute heroin self-administration prior to the 10-day period of continuous heroin use. This observation suggests development of tolerance with respect to heroin effects on LH levels. However, low testosterone levels per se could result in a stimulatory effect on LH as a consequence of long-loop feedback mechanisms which regulate LH secretory activity. A stimulating effect on LH secretory activity as a consequence of low testosterone levels could interact with a direct inhibitory effect of heroin at hypothalamic and pituitary sites. The relative contribution of these interacting factors on integrated plasma LH levels during chronic heroin use remains to be determined.

The most pronounced and dramatic effects of heroin on pituitary hormones was the prolactin response following acute and chronic heroin self-administration. Our data indicate that the magnitude and time course of prolactin response following heroin-self administration may provide a very useful index of assessing one aspect of opiate tolerance.

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Histopathologic and Clinical Abnormalities of the Respiratory System in Chronic Hashish Smokers

Tennant, F. S., Jr.

ABSTRACT

Thirty chronic hashish smokers (mean age-20 years) with respiratory symptoms and six control subjects who were nonhashish smokers were evaluated by history, physical examination, bronchoscopy, and bronchial biopsy. Twenty-three (23) of 23 (100 percent) patients who smoked hashish plus cigarettes had one or more histopathologic abnormalities of basal cell hyperplasia, atypical cells, or squamous cell metaplasia. Only two of seven (28.6 percent) hashish smokers who smoked cigarettes, one of three (33.3 percent) cigarette smokers who smoked no hashish, and zero of three (0 percent) nonsmokers showed one or more of the same histopathologic lesions ($p<.05$). Hashish smoking when combined with cigarette smoking appeared to have more deleterious pulmonary effects than either hashish or cigarettes smoked alone, and the abnormal histopathologic lesions found in these smokers are identical to those frequently associated with later development of emphysema and carcinoma of the lung.

INTRODUCTION

There is accumulating evidence that marijuana and hashish have considerable pulmonary effects.[1-13] Acute administration of marijuana has been found to increase bronchodilation and reduce bronchospasms induced experimentally in asthma sufferers.[4-8] Chronic administration, however, impairs lung function in otherwise healthy subjects, and there are studies which indicate that regular smoking of marijuana may result in cellular damage with permanent lung disease, such as interstitial fibrosis. Clinical reports describe bronchitis and pulmonary symptoms in hashish and marijuana smokers.[1-3]

An unanswered question is whether chronic marijuana or hashish smokers may develop emphysema or carcinoma of the lung in a manner analogous to cigarette smokers. Morphologic and cytochemical studies of marijuana smoke on lung epithelial cells show similar effects on deoxyribonucleic acid (DNA) and fibroblasts as does

cigarette smoke.[9,10] Mice and dogs subjected to chronic marijuana inhalation have been shown to produce squamous metaplasia and other pathologic changes of bronchial epithelial cells which are precursors of emphysema and carcinoma in cigarette smokers.[12,13] In an effort to partially determine if similar changes may occur in humans, thirty young males who chronically smoked high doses of hashish and had respiratory symptoms were clinically evaluated by history, physical examination, bronchoscopy, and biospy of the tracheobronchial mucosa. Their clinical and pathologic findings were compared to six young male subjects who did not smoke hashish or marijuana and who volunteered for bronchoscopy and biopsy of the tracheobronchial mucosa.

METHODS

Thirty (30) United States Army soldiers stationed in Wurzburg, West Germany sought medical assistance for one or more respiratory symptoms of cough, excess sputum production, chest pain, hemoptysis, or dyspnea (Table One). Ages of hashish smokers ranged from 17 to 22 years with a mean of 20.4 years. Every patient reported a hashish consumption of 25 to 150 grams per month for three to 24 months. Twenty-three (23) patients additionally smoked a mean of 1.0 pack of cigarettes per day for 1.5 to 12.0 years (mean-4.9 years). Seven (7) hashish smokers did not smoke cigarettes.

All patients completed a medical history which emphasized respiratory symptoms and smoking history. Each was given a physical examination and bronchoscopy with biopsies of the posterior wall of the trachea, approximately 0.5 cm. proximal to the carina and of the right and left mainstem bronchi. Each biopsy measured approximately 0.2 x 0.2 x 0.1 cm. and each was immediately placed in 10 percent formalin. At least ten paraffin sections of each were examined after staining with hematoxylin and eosin stains.

Findings were classified according to the method of Auerbach et al.[14,15] The respiratory epithelium was considered "normal" under the following conditions: there was no loss of cilia; there were one or two layers of basal cells; and no atypical cells were found. An abnormality was considered present if the epithelium appeared other than normal as defined above. Each abnormality was classified in one of the following categories: (1) basal cell hyperplasia when three or more layers of basal cells were present beneath a layer of columnar cells with or without cilia; (2) squamous metaplasia when the columnar epithelium has been replaced by a multilayered epithelium resembling stratified squamous epithelium. Atypical cells were defined as those whose nuclei exhibited hyperchromasia and whose nucleus cytoplasm ratios were increased. Nuclear pleomorphism, anisonucleosis, and increased numbers of mitoses may or may not have been present.

Findings in these patients were compared to six voluntary control subjects who did not smoke hashish and who were males from the same U.S. Army Post. Each of these subjects was given the same evaluation consisting of respiratory and smoking history, physical

examination, bronchoscopy, and tracheobronchial biopsy. Three of the control subjects were cigarette smokers ages 25, 32 and 26 years (mean-27.7 years) who had smoked a mean of 1.6 packs per day for ten to twelve years (mean-11.3 years). The other three volunteer subjects did not smoke hashish or cigarettes; their ages were 29, 22, 31 years (mean-27.3 years).

RESULTS

Twenty-two (22) of 23 (95.7 percent) hashish plus cigarette smokers, six of seven (85.7 percent) hashish only smokers, one of three (33.3 percent) cigarette smokers, and zero of three (zero percent) nonsmokers complained of a chronic cough ($p<.05$). No cigarette only or nonsmokers complained of any other respiratory symptom or showed any abnormality on physical examination or on gross examination during bronchoscopy. All hashish smokers, regardless of whether or not they smoked cigarettes, complained of one or more respiratory symptoms (Table One). Hashish-cigarette smokers reported more symptoms than hashish only smokers. Twelve (12) of 23 (52.2 percent) hashish-cigarette smokers compared to two of seven (28.6 percent) hashish only smokers complained of excess sputum production; 14 of 23 (60.9 percent) hashish-cigarette smokers compared to four of seven (57.1 percent) hashish only smokers complained of dyspnea (pNS); and five of 23 (21.8 percent) hashish-cigarette smokers compared to zero hashish only smokers complained of hemoptysis ($p<.05$). Physical examination revealed findings of ronchi, rales, or wheezes in 20 of 23 (87.0 percent) hashish-cigarette smokers and five of seven (71.4 percent) hashish only smokers (pNS). Gross examination of the tracheobronchial tree during bronchoscopy showed erythema and congestion in 13 of 23 (56.5 percent) hashish-cigarette and in zero of seven hashish only smokers ($p<.05$).

Histopathologic examination of bronchial biopsies reveal atypical cells in 23 of 23 (100 percent) hashish-cigarette smokers; two of seven (28.6 percent) hashish only smokers; one of three (33.3 percent) cigarette smokers and zero of three (zero percent) nonsmokers ($p<.05$). Basal cell hyperplasia was found in 14 of 23 (60.9 percent) hashish-cigarette smokers; one of seven (14.3 percent) hashish only smokers, and zero of six (zero percent) cigarette smokers or nonsmokers ($p<.05$). Squamous metaplasia was found in 21 of 23 (91.3 percent) hashish-cigarette smokers; one of seven (14.3 percent) hashish only smokers; one of three (33.3 percent) cigarette smokers, and zero of three (zero percent) nonsmokers ($p<.05$).

The only patient among the six control subjects who had a respiratory complaint or histopathologic abnormality was a 32-year-old cigarette smoker who had smoked at least two packs of cigarettes per day for 12 years.

DISCUSSION

Patients studied here chronically smoked large quantitites of hashish, which is known to be more irritating to the upper respira-

tory tract than is marijuana.[1,2] All 30 hashish smokers related one or more symptoms which compelled the patient to seek medical attention. Seven hashish smokers who did not additionally smoke cigarettes gave a history of fewer symptoms of excess sputum production, hemoptysis, or dyspnea. Hashish only smokers also appeared grossly normal during bronchoscopy and only two of seven (28.6 percent) had abnormal bronchial biopsies compared to 23 of 23 (100 percent) hashish-cigarette smokers ($p<.05$). Hashish only smokers, compared to three control subjects who only smoked cigarettes, appeared to exhibit no significant clinical or histopathologic differences, although hashish-cigarette smokers showed more clinical and histopathologic abnormalities than hashish only or cigarette only smokers. Nonsmoker control subjects showed no clinical or histopathologic abnormalities even though they were of slightly older ages.

It is possible that more control subjects who smoked only cigarettes may have showed one or more statistically significant differences with hashish only smokers, but the invasiveness of the biopsy technique limited the number of volunteer control subjects that could be recruited for study. This data, therefore, is not sufficient to determine if hashish only smoking is more detrimental than cigarette smoking to the pulmonary system. The findings indicate, however, that hashish plus cigarette smoking is more deleterious than smoking either one alone since one or more histopathologic abnormalities was found in 23 of 23 (100 percent) combination smokers compared to two of seven (28.6 percent) hashish only and one of three (33.3 percent) cigarette smokers ($p<.05$).

The histopathologic findings in these patients are compatible with previous reports which show that chronic marijuana inhalation may produce histopathologic changes in lung explants from mice and may produce squamous metaplasia in dogs and mice.[10,12,13] It is unknown if these abnormalities may possibly lead to emphysema or carcinoma of the lung, although this is a reasonable assumption since the histopathologic abnormalities found in these patients, particularly squamous metaplasia, have been shown to be associated with development of emphysema and carcinoma of the lung in cigarette smokers.[14,15] This study does not specifically study marijuana, but it is reasonable to assume that it too may produce similar histopathologic lesions in humans if smoked chronically with cigarettes.

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The opinions expressed here represent those of the author and not necessarily those of the U.S. Army.

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TABLE ONE

CLINICAL AND HISTOPATHOLOGIC FINDINGS IN HASHISH SMOKERS AND CONTROL SUBJECTS

	HASHISH PLUS CIGARETTES (N=23)	HASHISH WITHOUT CIGARETTES (N=7)	CIGARETTES ALONE (N=3)	NON-SMOKERS (N-3)	STATISTICAL SIGNIFICANCE
MEAN AGE IN YEARS	20.0	20.6	27.7	27.3	PNS
MEAN REPORTED HASHISH DOSAGE PER MONTH IN GRAMS	83.7	90.7	N/A	N/A	PNS
MEAN LENGTH OF HASHISH USAGE IN MONTHS	12.5	8.1	N/A	N/A	PNS
MEAN REPORTED LENGTH OF CIGARETTE CONSUMPTION PER MONTH IN PACKS	1.0	N/A	1.6	N/A	PNS
MEAN REPORTED LENGTH OF CIGARETTE CONSUMPTION IN YEARS	4.9	N/A	11.3	N/A	$P < .05$
CHRONIC COUGH	22 (95.7%)	6 (85.7%)	1 (33.3%)	0 (0%)	$P < .005$
EXCESS SPUTUM PRODUCTION	12 (52.2%)	2 (28.6%)	0 (0%)	0 (0%)	$P < .05$

TABLE ONE (CONTINUED)

CLINICAL AND HISTOPATHOLOGIC FINDINGS IN HASHISH SMOKERS AND CONTROL SUBJECTS

	HASHISH PLUS CIGARETTES (N=23)	HASHISH WITHOUT CIGARETTES (N= 7)	CIGARETTES ALONE (N=3)	NON-SMOKERS N=3)	STATISTICAL SIGNIFICANCE
DYSPNEA	14 (60.9%)	4 (57.1%)	0 (0%)	0 (0%)	$P < .10$
HEMOPTYSIS	5 (21.7%)	0 (0%)	0 (0%)	0 (0%)	PNS
RONCHI, RALES, AND/OR WHEEZES	20 (87.0%)	5 (71.4%)	0 (0%)	0 (0%)	$P < .05$
ERYTHEMA AND CONGESTION AT BRONCHOSCOPY	13 (56.5%)	0 (0%)	0 (0%)	0 (0%)	$P < .05$
BASAL CELL HYPERPLASIA	14 (60.9%)	1 (14.3%)	0 (0%)	0 (0%)	$P < .01$
ATYPICAL CELLS	23 (100%)	2 (28.6%)	1 (33.3%)	0 (0%)	$P < .05$
SQUAMOUS METAPLASIA	21 (91.3%)	1 (14.3%)	1 (33.3%)	0 (0%)	$P < .05$

Satellite Session on Khat

PHARMACOLOGY AND ABUSE POTENTIAL

Assessment of Public Health and Social Problems Associated With Khat Chewing

Khan, I.; Hughes, P. H.

We, in WHO, are grateful to the Committee on Problems of Drug Dependence for responding to our request to organize a symposium on khat during its 41st Annual Meeting. We are most gratified to note that four papers are being presented on the pharmacological effects of cathinone, and that Dr H. Halbach, formerly Director of the Division of Pharmacology and Toxicology at WHO/HQ., and Dr O. Braenden, Head of the UN Narcotic Laboratory at Geneva, are here to share with us their knowledge and long-standing experience gained in the subject over the years. The financial support provided to WHO by the United Nations Fund for Drug Abuse Control and which made this research possible is gratefully acknowledged. We look forward to working closely with the Committee, beyond investigations into the pharmacology of khat and into the field of epidemiology as well.

International research on khat spreads over three distinct phases. The first related to the study of the pharmacological effects of khat extracts and (+) cathine (norpseudephedrine) and the comparison of their effects with amphetamine-like substances. The second phase is related to extensive research by the UN Narcotics Laboratory on the chemistry of khat using freshly frozen khat leaves. This has led to the isolation of 30 substances, including cathinone, and was carried out in response to a request from the UN Commission on Narcotic Drugs in 1971. The availability of these substances has made it possible for WHO to stimulate research on the biological effects, especially its stimulant and reinforcing properties, in various countries around the world. The third phase of the research is related to assessing the public health and social problems associated with khat chewing in the environments where its use is prevalent. This type of study is a pre-requisite for decision-making by Governments and International Organizations on whether national and international controls are indicated for khat, and if they are needed, the most appropriate framework for those controls.

To initiate these studies, WHO has communicated to the concerned governments in its Eastern Mediterranean and African

regions to determine whether they would like to collaborate with WHO in assessing the public health and social problems related to khat chewing. On receiving positive responses, and with financial support from UNFDAC, WHO will implement the epidemiological phase of this international programme of research on khat.

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Khat—The Problem Today

Halbach, H.

The khat plant (catha edulis), a perennial shrub, has been cultivated for more than half a millennium in Ethiopia, Kenya, Tanzania, North Yemen, and more recently Madagascar. The leaves are chewed, but not normally swallowed, thus allowing for buccolingual or enteral absorption of soluble ingredients. The clinical effects of chewing khat have been well described in the ancient Arabic literature. In the main they can be referred to a phenylethylamine-type substance and tannins (0,1-0,2 percent and approximately 10 percent respectively in dry leaves.

The pharmacologically active constituent named cathine was identified by WOLFES (1930) as (+)norpseudoephedrine. Its peripheral and central effects are amphetamine-like, with greater potency of the dextrorotatory isomer of cathine as well. The potency of cathine was estimated to range between those of caffeine and amphetamine.

Khat users seek out the freshest possible plant material, an indication of the rapid degradation of cathine in the plant or, more likely, the existence of a more potent substance, possibly a precursor of cathine.

Although for purposes of introducing control measures the nature of khat effects can be satisfactorily explained as those of cathine, and although not these effects as such, but rather their consequences are likely to lead to public health and social problems warranting some kind of international control - not to mention the impracticability of controlling khat under the Convention on Psychotropic Substances- it was nevertheless decided that the active principle(s) of khat should be fully elucidated before contemplation of control measures.

The United Nations' Narcotics Laboratory succeeded in isolating, besides numerous inactive substances, 1) a series of so-called cathedulines (high-molecular-weight polyester-type alkaloids) one of which is chemically related to the sedative cassinin, but unlikely to interfere with the stimulating action of khat; 2) norephedrine; 3) cathine in low quantity; 4) (-)-α-amino-propiophenone "cathinone" in larger, but varying amounts. Whether the highly unstable cathinone

is a natural precursor of cathine is uncertain although its asymmetric carbon presents the same configuration as the corresponding nucleus in cathine which would be compatible with its conversion into the latter. Cathinone has been synthetized. Its N-diethylated derivative is amfepramone. The amphetamine-like pharmacological profile of cathinone has been studied by KNOLL and its reinforcing properties by SCHUSTER (to be reported by the authors).

The clinical effects of khat can be fully explained by its main constituents cathine/one and tannins. They include mydriasis, tachycardia, extrasystoles, elevated blood pressure, transient facial and conjunctival congestion, headaches, hyperthermia, increased respiration (through central stimulation, bronchodilatation, counterregulation of hyperthermia), inhibition of micturition, increased diuresis (from intake of large quantities of fluids together with khat); cerebral hemorrhage, myocardial insufficiency, pulmonary oedema in predisposed individuals. Increased sympathicotonus is believed to be, besides psychological khat effects, the cause of anaphrodisia and spermatorrhoea. Effects on the gastrointestinal tract include stomatitis, gingivitis, oesophagitis, gastritis, proneness to buccal and oesophageal epitheliomas and duodenal ulcers. Very common is constipation, sometimes with paralytic ileus. Anorexia as a typical amphetamine effect is a strong factor in the vicious circle khat-anorexia-malnutrition-digestive troubles-hunger-its suppression through khat ---. Malnutrition may aggravate intercurrent disease, e.g., tuberculosis.

The reinforcing effects of khat include euphoria, logorrhoea, improvement of associations, excitement, insomnia. Toxic psychosis occurs very rarely, if at all. This and the absence of tolerance is obviously due to the self-limiting process of ingestion. Symptoms of withdrawal from khat are rebound phenomena rather than the expression of a true physical dependence.

While the qualitative similarity between khat and amphetamines is evident the quantitative differences are probably of a pharmacokinetic nature yet to be explored.

Khat problems hardly existed when its use was acculturated as, e.g., with the Mehru and Isiolo tribes in Kenya where only the elder herdsmen were permitted to chew khat. The major contemporary problem of the excessive consumption of khat is the decrease of economic productivity through reduction of working hours spent on chewing khat as well as overspending for a non-essential commodity on the expense of food with ensuing malnutrition and proneness to disease and last, but not least, loss of needed foreign currency.

The problem is one of today because of the easy access to khat through air transport and because the economic development of khat-consuming countries cannot tolerate the loss of productivity from the excessive use of khat.

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Research on the Chemical Composition of Khat

Braenden, O. J.

At its 24th session, the Commission on Narcotic Drugs requested that the United Nations Narcotics Laboratory should carry out research on the chemical composition of khat, such research being fundamental for the subsequent evaluation of the effects on health and society caused by the chewing of khat.

Early literature on the chemistry of khat gives no information on the degree of freshness of the material used. This is an important factor because, in practice, khat is used only when fresh. Until recently the only well-characterized component of khat was cathine ((+)-norpseudoephedrine). The stimulating effects obtained from the chewing of khat were associated exclusively with the presence of cathine, but this could not be substantiated because of marked differences between the activities of fresh material and cathine.

The UN Laboratory therefore made an intensive study of the chemical composition of khat, using fresh material. Staff members visited Kenya, Madagascar, and the Yemen Arab Republic where they purchased fresh khat and immediately extracted this with suitable solvents. At the same time, khat material was freeze dried.

Thin layer and gas chromatographic analysis of extracts showed the presence of a number of nitrogen-containing components that were previously unknown in the plant. These compounds were separated into two major groups: the phenylalkylamine derivatives and the weakly basic alkaloids.

A study of the phenylalkylamine fraction showed that, in fresh or well-preserved khat material, cathine was only a minor component. However, in each sample, a new compound was found and its chemical structure was established as (-)-α-aminopropiophenone. As this compound had not previously been reported in nature, it was tentatively assigned the designation "cathinone". Cathinone base is very unstable and easily undergoes decomposition reactions leading to the formation of a "dimer" (3,6-dimethyl-2,5-diphenylpyrazine) and possibly smaller fragments such as benzaldehyde and ethylamine. Further decomposition may lead to 1-phenyl-1,2-propanedione. Both the "dimer" and the latter compound have been isolated from khat

extracts. The absolute configuration of cathinone was established by Schorno and Steinegger 1978. The UN Laboratory also synthesized racemic cathinone using the method of Gabriel 1908, with some modifications. From this, the optically active isomers and the "dimer" were prepared. Other minor compounds were also identified in the amine fraction.

The fraction containing the weakly basic alkaloids was found to have a very complex composition. More than forty alkaloids have so far been detected in khat by thin layer chromatography. Some of the major components in this group were isolated. Structures were proposed for eleven alkaloids and further structures are being established. In this work, the UN Laboratory collaborated closely with Professor L. Crombie and his group at the University of Nottingham, where considerable work has been done in this field (Baxter et al. 1976, Crombie et al. 1978). With two exceptions, all the alkaloids thus far isolated from khat have had a common hydroxylated sesquiterpene skeleton (euonyminol) which is esterified with various acids. The common name "cathedulin" was proposed for this class of alkaloids.

In November 1978, the UN Laboratory convened a group of experts to review present knowledge of the botany and chemistry of khat and to prepare guidelines for future research in these fields. The report of this group includes an annex listing all the substances that have been isolated from khat together with their structural formulae. The UN Laboratory is now concentrating its attention on the preparation of adequate amounts of certain khat components for the pharmacological studies being carried out under the auspices of the World Health Organization.

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Studies on the Central Effects of (-)Cathinone

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(-)Cathinone and (+) cathine are constituents of khat which were isolated from freeze-dried khat samples.(-) Cathinone is thought to be the major psychostimulant component in khat which might be of high importance in producing the medical effects of the chewing of khat leaves.For this reason the effect of (-)cathinone in comparison to (+) cathine and amphetamine was studied in a battery of in vivo tests:motility (mouse), oxygen consumption (rat), food intake (rat), one way avoidance (rat), writhing (mouse), hot plate (rat), nictitating membrane (cat) and flexor reflex (rat); and on isolated organs: the cat nictitating membrane, the rabbit central ear artery, rabbit pulmonal artery, guinea pig vas deferens and rat vas deferens.

(-)Cathinone was as potent as amphetamine in increasing locomotor activity in mice, it increased oxygen consumption like amphetamine, was more potent than amphetamine in inhibiting food intake in rats at intraventricular administration. All these effects could be antagonized by pretreatment of α-methylparatyrosine.

In the hot plate test, which is used for studying analgesics,(-)cathinone, (+)cathinone and cathine prolonged, like amphetamine, the reaction time in high doses. These effects were antagonized by α-methylparatyrosine and are apparently the consequence of overexcitataion. None of these compounds is real analgesic. Analgesics act in lower doses on the writhing test than in the hot plate.Both isomers of cathinone acted only in very high doses in the writhing test, showing that these compounds are not real analgesics.

The flexor reflex of the hind limb of the spinal rat, elicited by hind paw stimulation, is controlled by noradrenergic transmission and is regarded as a good model

for studying the action of drugs on central noradrenergic neurones. Amphetamine (1 mg/kg, i.v.) stimulates the responses. Both isomers of cathinone were found to be as potent as amphetamine in this test; cathine proved to be less potent than cathinone.

Amphetamine (0,25-1 mg/kg, i.v.) elicits a long-lasting contraction of the nictitating membrane in the cat, and tolerance to the effect of a single dose develops. (-)Cathinone acts like amphetamine and cross tolerance between these amines was observed.

In isolated organs with noradrenergic neurotransmission, (-)cathinone facilitated neuromuscular transmission like amphetamine and desmethylimipramine inhibited these effects. On isolated rat vas deferens preparations (-)cathinone, (+)cathine, amphetamine and phenylethylamine (PEA) were found to be about equally potent in the facilitation of field stimulated contractions. On the guinea pig vas deferens preparation PEA and amphetamine were found to be more potent than (-)cathinone and (+)cathine on the perfused rabbit ear artery. (-) Cathinone was more potent than amphetamine on the rabbit pulmonal artery strip, amphetamine and (-)cathinone were found to be usually equally active, no tolerance to the effects of amphetamine, (+)cathine and (-)cathinone were found on the vas deferens preparations and on the isolated arteries. On the other hand, tolerance develped to the effect of amphetamine, (+)cathine and (-) cathinone on the isolated medial smooth muscle of the cat nictitating membrane and cross-tolerance between these amines was observed. No tolerance to the effects of PEA was observed on this organ, but on a preparation which developed tolerance to amphetamine or to (-)cathinone, also PEA lost completely its effect.

According to the in vivo and in vitro experiments the main acute effect of (-)cathinone and (+)cathine is the facilitation of noradrenergic transmission. Like amphetamine, they are taken up by the noradrenergic nerve terminals and, with high probability, release the transmitter from extravesicular pools.

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Behavioral Studies of Cathinone in Monkeys and Rats

Schuster, C. R.; Johanson, C. E.

As has been pointed out by previous speakers, it is now apparent that the principal pharmacologically active agent in the Khat plant is l-cathinone.

For the last year our laboratory has been investigating the behavioral actions of dl-and l-cathinone. Because cathinone is structurally and pharmacologically similar to d-amphetamine, these studies have attempted to compare the effects of cathinone to those of d-amphetamine.

To date, three behavioral procedures have been used. These are: 1) food-reinforced responding in rhesus monkeys, 2) drug self-administration in monkeys 3) studies of tolerance and cross-tolerance to the anorexic effects of cathinone and d-amphetamine in rats.

I. FOOD REINFORCED RESPONDING IN RHESUS MONKEYS

Three rhesus monkeys were trained to lever press under a multiple fixed-interval (FI) 5 min. fixed-ratio (FR) 30 schedule of food delivery. Specifically, in the presence of a red light animals were reinforced for the first response occuring after five minutes had elapsed from the preceding food delivery. Following completion of the FI component, the stimulus lights turned green and the animals were reinforced with food after completion of 30 lever presses. The FI and FR components alternated throughout a two hour daily session.

After behavior stabilized under the multiple schedule, dose-response curves were obtained for d-amphetamine and dl-and l-cathinone. Doses of drugs were given intravenously 5 minutes before selected daily drugs.

All three drugs produced a dose-related decrease in responding under both the FI and FR conditions. dl-and l-Cathinone appeared to be approximately equal in potency whereas d-amphetamine was twice as potent.

II. DRUG SELF-ADMINISTRATION STUDIES

Three rhesus monkeys surgically prepared with indwelling venous catheters served as subjects. All animals had been previously trained to lever press under an FR 10 schedule of cocaine delivery during a 3-hr daily session. Various doses of d-amphetamine, dl-

and l-cathinone as well as saline were substituted for cocaine for 5 consecutive sessions. All drugs maintained responding at levels significantly above those seen when saline was substituted. Both dl-and l-cathinone maintained rates of responding significantly higher than those generated by cocaine and d-amphetamine. Further, l-cathinone appeared to be more potent than either dl-cathinone or d-amphetamine.

III. TOLERANCE STUDIES

In two separate studies, cross-tolerance between d-amphetamine and dl-cathinone was studied. In these studies, the anorexic effects of the two drugs were studied in rats by determining their efficacy in decreasing the animal's intake of sweetened condensed milk made available for 15 minutes on a daily basis. Both d-amphetamine and dl-cathinone produced a dose-related decrement in milk intake. In both studies dose-response curves for both drugs were obtained before, during and after a period of repeated administration of drug. In the first study, d-amphetamine (2.0 mg/kg/) was given daily. In the second study, dl-cathinone was given daily. In both studies, tolerance was demonstrated by a diminution in the effect of the chronically administered drug and as well by a shift in the dose-response curve to the right. In the case of d-amphetamine, this shift was approximately two-fold whereas with dl-cathinone, a much larger shift was obtained (8-12 fold). In both studies cross-tolerance between dl-cathinone and d-amphetamine was observed.

In summary, dl-cathinone shares with d-amphetamine the ability to: 1) disrupt food reinforced lever pressing behavior in monkeys; 2) serve as a positive reinforcer in drug self-administration experiments; 3) produce a decrement in milk intake in rats; and 4) produce tolerance to its anorexic effects. In addition, there is cross-tolerance between cathinone and amphetamine.

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Studies on Cathinones: Cardiovascular and Behavioral Effects in Rats and Self-Administration Experiment in Rhesus Monkeys

Yanagita, T.

Three types of pharmacodynamic studies were conducted on cathinones.

1. CARDIOVASCULAR EFFECTS IN RATS AND ISOLATED ATRIA OF GUINEA PIGS

In intact rats, both l- and dl-cathinone produced exophthalmos, piloerection, and sniffing at doses of 4 mg/kg, s.c. or higher. d-Amphetamine produced such effects at 1 mg/kg, s.c.

In anesthetized rats, both blood pressure and heart rate were increased. At a single dose of 1 mg/kg, i.v., the average pressure increases were: d-norpseudoephedrine, 24.0±5.8; l-cathinone, 15.7±1.4; dl-cathinone, 11.4±4.1; dl-ephedrine, 24.8±3.7; and d-amphetamine, 21.5±1.8 mmHg; and the heart rate increases were: 49.5±5.1, 50.0±10.1, 41.2±10.1, 55.7±6.4 and 58.7 ±8.7 beats/min respectively.

In isolated guinea pig atria, at a bath concentration of 10^{-5} g/ml, positive ionotropic and chronotropic effects were observed with the cathinones. The average percent increases of the ionotropic effects were: l-cathinone, 83.3±4.8; d-norpseudoephedrine, 52.8±10.7; dl-cathinone, 42.4±7.6; dl-ephedrine, 36.7±9.6; and d-amphetamine, 50.5±9.1

2. BEHAVIORAL EFFECTS

In a spontaneous motor activity test in rats, dl-cathinone increased the activity level markedly at a dose range of 0.25 to 4.0 mg/kg, s.c. The potency of the effect was almost comparable to that of d-amphetamine. dl-Ephedrine did not produce such marked effects at doses up to 16.0 mg/kg, s.c.

The operant behavioral effect of dl-cathinone was tested under a DRL 20 sec schedule for food reinforcement in rats. Like d-amphetamine, this drug increased the response rate, decreased the

reinforcement rate and markedly shortened the interresponse time-intervals at doses higher than 0.5 mg/kg, s.c. dl-Ephedrine had no such effect, excepting decrement of the reinforcement rate which was noted at 16.0 mg/kg, s.c.

3. INTRAVENOUS CONTINUOUS SELF-ADMINISTRATION EXPERIMENT IN RHESUS MONKEYS

Two monkeys initiated intravenous self-administration of l-cathinone at a unit dose of 0.06 or 0.25 mg/kg/injection. The self-administration pattern was of the spree type, like cocaine, in which the monkeys took the drug frequently day and night, stopping upon becoming exhausted. Such sprees continued from several hours to 2-3 days, and during these periods the monkeys manifested extreme restlessness, tremor, mydriasis, and anorexia. They relapsed after a period of rest of within 24 hours. This alternation of spree and rest was repeated, but the experiment had to be terminated within a month due to general weakening in one monkey and edema in the other. The duration of each spree and the average hourly doses self-administered during each spree were as follows: monkey No. 1006: 1st spree 9 hrs, 0.8 mg/kg (0.06 mg/kg/inj); 2nd spree 32 hrs, 1.1 (0.06); 3rd spree 6 hrs, 1.0 (0.06); 4th spree 53 hrs, 1.9 (0.25); 5th spree 59 hrs, 1.4 (0.25); monkey No. 607: 1st spree 6 hrs, 1.6 mg/kg (0.25 mg/kg/inj); 3rd spree 57 hrs, 3.2 (0.25); 5th spree 11 hrs, 5.5 (0.25); 7th spree 40 hrs, 4.8 (0.25).

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Discriminative Stimulus and Neurochemical Mechanism of Cathinone: A Preliminary Study

Rosecrans, J. A.; Campbell, O. L.; Dewey, W. L.; Harris, L. S.

The major emphasis of our research conducted with cathinone involved approaches attempting to elucidate its mechanism of action. The strategies employed involved two major studies, one in mice and a second in rats. In the first study, l- and d-cathinone were observed to increase spontaneous activity in mice in doses ranging from 4-16 mg/kg (I.P.). The l-isomer appeared more potent than the d-isomer in these activity procedures, and its effects were studied further on brain catecholamine turnover in a different group of mice. In addition, d-amphetamine's neurochemical effects were also evaluated using a similar dose range. l-Cathinone was observed to have little effect on norepinephrine (NE) turnover but did significantly increase dopamine (DA) turnover at 8 mg/kg (+32%). In contrast, d-amphetamine reduced NE turnover at similar doses but also increased DA turnover (44%) at 4 mg/kg. At higher doses, dl-cathinone (16 mg/kg) had little effect on DA turnover while d-amphetamine produced a 42% reduction. These studies indicated that dl-cathinone produced CNS stimulant effects and did resemble d-amphetamine by increasing DA turnover at 8 mg/kg. However, l-cathinone in the dose range studied did not appear to be as potent as d-amphetamine in altering catecholamine turnover.

In the second series of experiments, dl-cathinone was studied in rats using a two-lever drug discrimination procedure. In this paradigm, subjects were trained to discriminate between the effects of d-amphetamine (0.9 mg/kg, I.P.) and saline in order to obtain a food reinforcement. In the specific experiments conducted, the discriminative stimulus effects of d-amphetamine were compared to those produced by dl-cathinone. d-Amphetamine trained rats responded as if they were given d-amphetamine when various doses of dl-cathinone were administered (I.P.). This generalization was dose related and dl-cathinone (ED_{50}=0.09 mg/kg) was observed to be twice as potent as d-amphetamine (ED_{50}= 0.19 mg/kg). Thus, dl-cathinone produced stimulus effects similar to d-amphetamine. We next set out to determine whether the mechanism of action of both drugs was similar. The first approach used was to determine whether the DA antagonist

haloperidol would be effective in reducing both stimuli. Interestingly, 0.1 mg/kg of haloperidol increased d-amphetamine's ED_{50} value from 0.190 (0.11-0.33) to 0.737 (0.53-1.04) mg/kg but had no effect on the generalization of the d-amphetamine stimulus to dl-cathinone. Thus, while dl-cathinone and d-amphetamine were indistinguishable behaviorally, their mechanism of action appeared quite different. We studied several other antagonists including the α-adrenergic antagonist, phenoxybenzamine, and the serotonin antagonists, BC105/B, but none of the drugs studied were able to antagonize either stimulus effect.

dl-Cathinone appears to be a very interesting stimulant compound. It produces behavioral effects similar to d-amphetamine, but may not be acting upon DA systems as does d-amphetamine. This finding, while academically important, has some practical significance as well. The studies presented by Schuster (this Symposium) clearly indicated that dl-cathinone is self-administered at lower doses than d-amphetamine, but was less effective than d-amphetamine in disrupting the operant behavior of primates. One hypothesis generated in this laboratory over the last couple of years suggests that behavioral disruption produced by drugs such as d-amphetamine and morphine is related to their agonist effect on DA neurons. Taking this into consideration, the data presented here concerning dl-cathinone's would predict that this drug would be less able to disrupt behavior than d-amphetamine as was demonstrated. Thus, dl-cathinone appears less disruptive to behavior, which might explain why this drug was more potent than d-amphetamine in our discrimination study and in self-administration research. From this, one might also predict that individuals using this drug would be less disrupted and better able to function under its effects. In addition, this drug might produce fewer long term d-amphetamine-like behavioral problems because of its apparent lack of a DA agonist action. However, this is not to say that cathinone could not produce psychological problems following chronic administration.

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Progress Reports

Annual Report: Dependence Studies of New Compounds in the Rhesus Monkey (1979)

Aceto, M. D.; Harris, L.S.; Dewey, W. L.; May, E. L.

All the test drugs were supplied by Dr. Arthur Jacobson, Medicinal Chemistry Section, NIAMDD, under the auspices of the Committee on Problems of Drug Dependence, Inc. Morphine was supplied by Dr. Robert Willette, NIDA. The chemical structures of the test compounds excluding (+)-naloxone and yohimbine were unknown to us at the time that they were tested.

Three mouse tests were used in our laboratory at the Medical College of Virginia to provide a preliminary estimate of the potency and profile of activity of each test compound. The tests were the tail-flick agonist (TF) and the morphine antagonist tests (TF vs M) and the phenylquinone test (PPQ)(Dewey et al, 1970; Dewey and Harris, 1971). Reference standard data for these tests are shown in table 1. In addition, Dr. Jacobson supplemented these data with estimated starting doses which were based on results obtained from the mouse hot plate (HP)(Eddy and Leimbach, 1953; Jacobson and May, 1965; Atwell and Jacobson, 1965) and Nilsen (N)(Perrine et al, 1972) tests from his laboratory. Reference data for these tests are shown in table 2.

These studies were supported by a contract (#271-77-3404) from the National Institute on Drug Abuse, Dr. Heinz Sorer, Contract Officer. The authors gratefully acknowledge the technical assistance of F. Tom Grove and R. F. Jones.

For the most part, the procedures described by Seevers and his colleagues (1936, 1963) and Deneau (1956) regarding the facilities and training of the monkeys were used and a brief description follows. The monkeys were injected with 3 mg/kg/sc of morphine sulfate every 6 hours for at least 90 days before being used. This dose schedule was reported by Seevers and Deneau (1963) to produce maximal physical dependence. Modified procedures for the precipitated withdrawal test (PPt-Withdrawal) and single dose suppression test (SDS) were reported by Aceto and coworkers (1974, 1977 and 1978). The PPt-Withdrawal test was initiated by the injection of a test drug 2 1/2 hours after an injection of morphine and the animals were observed for signs of withdrawal. The SDS test was started approximately 15 hours after the last dose of morphine at which time the animals were showing withdrawal signs. The test compound was injected and the animals were observed for the suppression of abstinence signs. The onset and duration of action of the test drug were noted. In both tests, a vehicle control and an appropriate positive control (naloxone 0.05 mg/kg or morphine sulfate 3.0 mg/kg) along with 3 different treatments (doses) of a test compound were randomly allocated to the 5 monkeys of a group. Occasionally 4 monkeys comprised a group and 2 doses of test compound were studied. Usually, 3 or 4 groups per compound were used. All drugs were given subcutaneously in a volume of 1 ml/kg and the vehicle used is indicated for each compound. The observer was "blind" with regard to the treatment given. A minimum 2-week washout and recuperation period between tests was allowed. In the primary physical dependence test, the animals of a group received the drug every 6 hours for 30-45 days. They were placed in abrupt withdrawal and challenged with naloxone periodically, and were observed for signs of physical dependence.

Table 1

Comparative Data - ED_{50} Mg/Kg/Sc (95% C.L.) of Selected Standards in 3 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick Test	Tail Flick Antagonism Test	Phenylquinone Test
Pentazocine	15% at 10.0	18(12.4-26)	1.65(1.0-2.5)
Cyclazocine	17% at 1.0[a]	0.03(0.12-.78)	0.011(0.0046-0.3)
Nalorphine .HCl	None at 10.0	2.6(0.69-9.75)	0.6(0.25-1.44)
Naloxone .HCl	None at 10.0	0.031(.010-0.93)	No Activity
Naltrexone .HCl	None at 10.0	0.007(0.002-0.02)	No Activity
Morphine Sulfate	5.8(5.7-5.9)	----	0.23(0.20-0.25)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but no further increase in reaction time was seen.

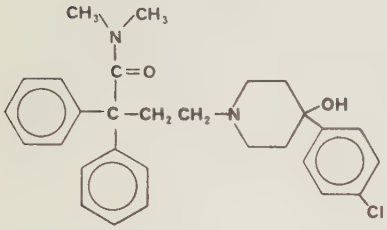
Table 2

Comparative Data (ED_{50s} Mg/Kg) (95% S.E.) from the Hot Plate and Nilsen Test

Compound	Hot Plate Test	Nilsen Test
	Subcutaneous	Subcutaneous
	Oral	Oral
Morphine Sulfate	1.0(0.7-1.4)	0.7(0.5-1.1)
	6.3(4.7-8.3)	8.3(6.0-11.4)
Codeine Phosphate	6.8(4.5-10.2)	7.4(4.9-11.0)
	13.5(9.7-18.7)	14.7(9.2-23.3)
Levorphanol Tartrate	0.2(0.1-0.3)	0.2(0.16-0.3)
	-	2.5(1.7-3.7)
Meperidine .HCl	4.6(3.3-6.4)	3.5(2.3-5.4)
	-	-
(-)-Metazocine .HBr	0.6(0.5-0.9)	0.5(0.3-0.7)
	10.6(8.0-14.1)	26.0(21.0-33.0)
Dihydromorphinone .HCl	0.13(0.11-0.16)	0.2(0.15-0.3)
	0.9(0.7-1.2)	1.8(1.5-2.1)
Nalorphine .HCl	9.9(5.7-17.1)	23.0(16.2-32.7)
	-	-
Cyclazocine	2.0(1.4-2.8)	0.1(0.07-0.16)
	-	-
Pentazocine	9.0(6.5-12.4)	6.5(4.4-8.8)
	-	-
Chlorpromazine .HCl	1.1(0.9-1.5)	-
	3.2(2.4-4.2)	
Naloxone .HCl	No Dose Response	-
Naltrexone .HCl	No Dose Response	-

Phenobarbital, Amobarbital, Valium, Meprobamate and Mescaline are inactive on the hot plate test.

MCV 4073-NIH 8635, 8714, 9230-UM 884, 899. 4-(p-Chloro-phenyl)-4-hydroxy-N,N-dimethyl-alpha, alpha-diphenyl-1-piperidinebutyramide hydrochloride (Loperamide)



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-28% at 10.0 at 20 min.; 92% at 10.0 with 1 hr pre-medication

2) TF vs M - Inactive at 1.0, 3.0, 10.0 and 30.0

3) PPQ-0.3 (0.1-0.7)

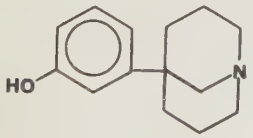
4) HP-2.6 (2.1-3.2)

MONKEY DATA (SDS)	# Animals				
	Doses(mg/kg/sc)	1 10.0	3 5.0	3 2.5	2 1.25

Vehicle - 50% propylene glycol - v/v.

Results: MCV 4073 substitutes completely for morphine. The drug appears to be as potent as morphine with a similar onset and duration of action.

MCV 4075-NIH 9234. 5-(3-Hydroxyphenyl)-3-azabicyclo (3.3.1) nonane hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF - Inactive at 1.0, 3.0 and 10.0

2) TF vs M - Inactive at 1.0, 3.0, 10.0; 28% at 30.0

3) PPQ-7.7 (0.5-11.7)

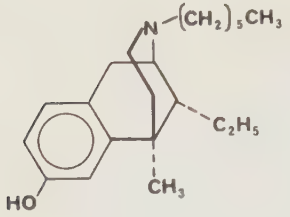
4) HP-15.8 (11.2-22.4)

MONKEY DATA (PPt Withdrawal)	# Animals				
	Doses(mg/kg/sc)	1 20.0	3 10.0	3 5.0	2 2.0

Vehicle H_2O.

At 10.0 mg/kg the drug precipitated withdrawal signs. The onset of action was rapid (< 30 min) and the duration of effect was at least 2 1/2 hours. However, at the highest dose severe tremors and convulsions were seen which were terminated by an injection of 60 mg of pentobarbital. The main sign observed at the 2 lower doses was drowsiness. Drug supply was exhausted.

MCV 4084-NIH 9261. 9α-Ethyl-2-hexyl-2'-hydroxy-5-methyl-6-7-benzomorphan



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-18.7 (9.5-37.0)

2) TF vs M -Inactive at 1.0, 3.0, 10.0 and 30.0

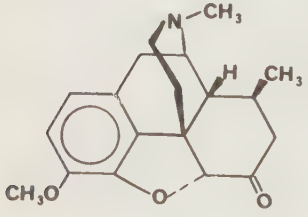
3) PPQ-5.7 (3.1-10.4)

4) HP-6.2 (4.5-8.5)

MONKEY DATA
(Primary Physical Dependence)

Five non-dependent monkeys were injected every 6 hours with MCV 4084. The drug was dissolved in lactic acid and H_2O. On the first day, the animals received 3.0 mg/kg/sc and by day 12 the dose had been raised to 14.0. The study terminated at this time because severe lesions developed at the sites of injections. A wide variety of signs designated as restlessness, scratching, ataxia, salivation, retching, vomiting and tremors were noted. On 2 occasions, convulsions were also seen. When the animals were placed in abrupt withdrawal, signs designated as avoids contact, vocalizes, restless, tremors, retching, and vocalizes when abdomen palpated were recorded from 12-16 hours after the last dose. A naloxone challenge of 0.5 mg/kg/sc was given and withdrawal seemed to be exacerbated. MCV 4084 appears to produce morphine-like physical dependence.

MCV 4106-NIH 9352. 8β-Methyldihydrocodeinone hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-5.9 (3.3-10.5)

2) TF vs M -Inactive at 10.0 and 30.0

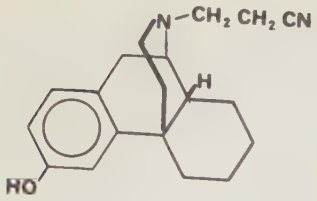
3) PPQ-0.5 (0.2-1.3)

4) HP-1.2 (0.8-1.7)

MONKEY DATA (SDS) # Animals Doses(mg/kg/sc) $\frac{3}{2.0}, \frac{3}{1.0}, \frac{3}{0.5}$; Vehicle H_2O.

Results: MCV 4106 substituted completely for morphine. At the lowest dose the duration of action was approximately one hour. At 1.0 mg/kg the duration of action was approximately 2 hrs and at the highest dose the effect was still evident 3 hrs after drug. The drug appears to be as potent as morphine.

MCV 4107-NIH 9354. ß-(-)-N-(2-Cyanoethyl)-3-hydroxymorphinan



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-5.9 (3.3-10.5)

2) TF vs M -Inactive at 10.0 and 30.0

3) PPQ-0.5 (0.2-1.3)

4) HP-0.02 (0.02-0.34)

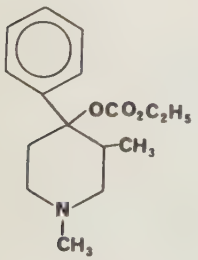
5) N-0.05 (0.03-0.07) (Oral=3.5 [2.3-5.3])

MONKEY DATA
(Primary Physical Dependence)

Vehicle H_2O

Five non-dependent monkeys were given MCV 4107 every 6 hours. The animals were observed for overt changes and the results were recorded as designated below. At 0.05 mg/kg, the lowest dose, severe drug-induced effects were noted. The animals appeared drowsy, were frequently found lying on their sides or abdomens, showed body sag, ataxia, wet dog shakes and tremors, moved about slowly and had eyelid ptosis. When the dose was raised to 0.1 mg/kg the animals were nearly incapacitated and the dose was dropped to 0.05 mg/kg each time. The drug had a prompt onset and a short duration (2 hours) of action. Little, if any, tolerance developed. The animals were placed in abrupt withdrawal on day 33 and at the end of day 44 of the study restlessness, yawning, scratching and wet dogs were seen. Signs such as retching, vomiting, rigid abdomen and vocalization when abdomen was palpated were not observed. The drug does not produce typical morphine-like physical dependence.

MCV 4120-NIH 9264. 1,3-Dimethyl-4-phenyl-4-piperidylethyl carbonate



MOUSE DATA-ED_{50} (95% C.L.) -(mg/kg/sc)

1) TF-Supply exhausted

2) TF vs M -

3) PPQ -

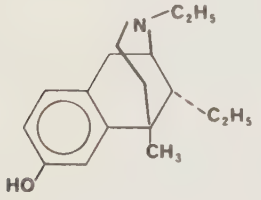
4) HP-11.9 (8.7-16.4)

MONKEY DATA (SDS)	# Animals	1	2	2	1
	Doses(mg/kg/sc)	24.0	16.0	8.0	4.0

Vehicle H_2O

At the 2 higher doses, MCV 4120 appeared to substitute completely for morphine. At 24.0 mg/kg the onset of action was rapid (less than 30 min) and the duration of action was under 150 min. Drug supply was exhausted. More studies are recommended.

MCV 4121-NIH 9258. 2,9-alpha-Diethyl-2'-hydroxy-5-methyl-6,7-benzomorphan



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF -Inactive at 1.0, 10.0 and 30.0

2) TF vs M -16.6 (12.2-22.6)

3) PPQ-22.9 (12.1-43.6)

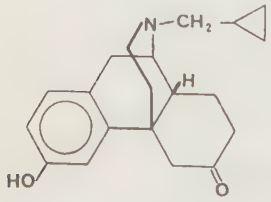
4) HP-21.3 (13.4-33.9)

MONKEY DATA (PPt-Withdrawal)	# Animals	1	2	2	1
	Doses(mg/kg/sc)	16.0	8.0	4.0	2.0

Vehicle H_2O

MCV 4121 precipitated withdrawal signs in the dose range tested. At the highest dose,(3 mg/kg) morphine was given to terminate severe withdrawal. Ataxia was noted in the animal receiving 16.0 mg/kg and in 1 of 2 monkeys receiving 4.0 mg/kg. Drowsiness was also observed in most of the animals. Drug supply was exhausted.

MCV 4130-NIH 9466-UM 1150. (-)-17-(Cyclopropylmethyl)-3-hydroxymorphinan-6-one methanesulfonate



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF - Inactive up to 30.0

2) TF vs M-0.4 (0.2-0.8)

3) PPQ-0.3 (0.1-0.6)

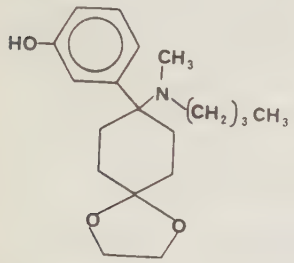
4) HP-17.2 (13.3-22.2)

MONKEY DATA (PPt-Withdrawal)	# Animals	2	3	2	1
	Doses(mg/kg/sc)	16.0	8.0	4.0	2.0

Vehicle H_2O

MCV 4130 precipitated withdrawal. The effects were dose-related. One monkey receiving the highest dose was found dead on the following day. The drug is approximately 1/80 as active as naloxone.

MCV 4131-NIH 9468. 4-(Methyl-n-butylamino)-4-(m-hydroxyphenyl)-cyclohexanone ethylene ketal hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-34.6 (12.7-93.9)

2) TF vs M-6.3 (1.5-26.6)

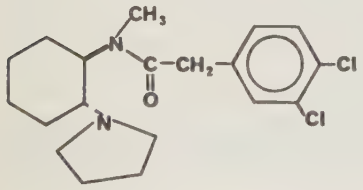
3) PPQ-8.5 (4.8-15.0)

4) HP-5.5 (3.8-7.8)

MONKEY DATA (SDS) # Animals Doses(mg/kg/sc) 6/8.0, 6/4.0, 6/2.0, Vehicle H_2O

This compound substituted partially and briefly for morphine at 4.0 mg/kg. One monkey given the highest dose was given morphine to terminate retching and vomiting. Possibly, the drug has a biphasic action. More studies are recommended. Partial substitution does not necessarily imply that the drug has morphine-like properties.

MCV 4133-NIH 9470. (±)-trans-N-Methyl-N-(2-pyrrolidinyl) cyclohexyl)-2-(3,4-dichlorophenyl) acetamide HCl



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-10.3 (2.7-40.2)

2) TF vs M -Inactive at 30.0

3) PPQ-0.8 (0.3-1.9)

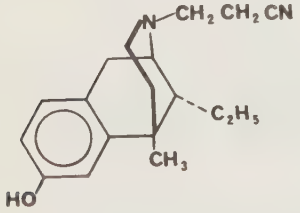
4) HP-8.3 (5.7-12.1)

MONKEY DATA
(Primary Physical Dependence)

Five drug-naive monkeys were given MCV 4133 sc dissolved in H_2O every 6 hours. The starting dose was 0.5 mg/kg. At doses up to 6.0 mg/kg, which was reached by day 10, the principal signs noted in all animals were drowsiness and eyelid ptosis. When the dose was increased to 10.0 mg/kg the animals slowed considerably and showed body sag and salivation. They appeared ataxic and showed tremors as the dose was raised. Because of the severe side effects, the dose was lowered first to 7.0 and then 6.0 mg/kg

from days 16-29. Body sag, salivation, tremors eyelid ptosis and drowsiness were seen regularly when the dose was again increased to 8.0 mg/kg from days 30-37. The signs designated drowsiness, eyelid ptosis, tremors, body sag and ataxia were seen consistently throughout the remainder of the study in which the dose was gradually raised to 16.0 mg/kg by day 48. At 15 and 30 days, the animals were challenged with naloxone (0.05 mg/kg/sc) but few signs were seen. When the animals were placed in abrupt withdrawal at the end of the study, some restlessness, wet dogs, fighting and coughing were seen. Fifteen days after abrupt withdrawal the animals were challenged with naloxone (5.0 mg/kg) and some restlessness, yawning, wet dogs and drowsiness were seen. Weight changes throughout the study were not remarkable. The onset action was rapid and the duration of action was from 2-4 hours. The drug does not produce a significant degree of morphine-like physical dependence. Little tolerance developed.

MCV 4137-NIH 9484. 2-(2-Cyanoethyl)-9-alpha-ethyl-2'-hydroxy-5-methyl-6,7-benzomorphan



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

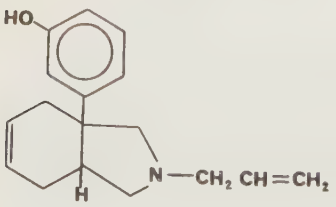
1) TF-0.8 (0.4-1.5)
2) TF vs M -Inactive at 1.0, 3.0 and 30.0
3) PPQ-0.09 (0.04-0.2)
4) HP-0.21 (0.16-0.30)

MONKEY DATA (SDS)	# Animals					
	Doses(mg/kg/sc)	2 / 2.4	3 / 1.2	4 / 0.6	2 / 0.5	1 / 0.3

Vehicle - Carboxymethylcellulose suspension

MCV 4137 substituted partially for morphine beginning at 1.2 mg/kg. The signs of retching, vomiting, vocalizes when abdomen palpated, rigid abdomen and pacing were suppressed. Recommended that additional studies be done at higher doses.

MCV 4140-NIH 9506-UM 1155. 2-Allyl-3a-m-hydroxyphenyl-2,3,3a,4,7,7a-hexahydro-cis-isoindole



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

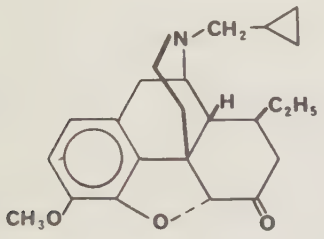
1) TF - Inactive at 1.0, 3.0 and 10.0
2) TF vs M - 0.55 (0.09-3.4)
3) PPQ-30.7 (8.7-103.0)
4) HP-Inactive
5) N-Inactive

MONKEY DATA (SDS) # Animals 3, 3, 3
Doses (mg/kg/sc) 8.0, 4.0, 2.0,

Vehicle - carboxymethylcellulose

MCV 4140 did not substitute for morphine in the dose range tested. The drug may have exacerbated withdrawal.

MCV 4142-NIH 9508. N-Cyclopropylmethyl-8-beta-ethylnordihydrocodeinone hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

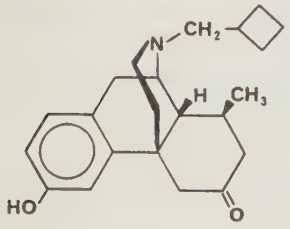
1) TF- Inactive at 1.0, 3.0 and 10.0
2) TF vs M-0.2 (0.03-1.5)
3) PPQ-18.0 (7.5-43.6)
4) HP-16.8 (1.05-26.9)
5) N-50% at 50.0 and 100.0

MONKEY DATA (PPt-Withdrawal) # Animals 2, 2, 2,
Doses (mg/kg/sc) 24.0, 12.0, 6.0

Vehicle H_2O

MCV 4142 precipitated withdrawal at all the doses tested. One monkey receiving the highest dose and another receiving the intermediate dose still showed withdrawal signs 7 hours later even though morphine had been given to them. On the second day in another group of monkeys, all those receiving MCV 4142 were given morphine after 20 minutes to terminate severe withdrawal. The drug appeared to have a long duration of action.

MCV 4143-NIH 9509. N-Cyclobutylmethyl-3-Hydroxy-8-beta-methyl-6-oxomorphinan tartrate



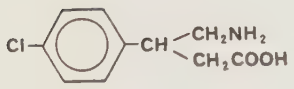
MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-24.0 (4.7-123.8)
2) TF vs M-0.4 (0.06-2.3)
3) PPQ-0.01 (0.004-0.05)
4) HP-3.05 (2.1-4.4)

MONKEY DATA (SDS) # Animals 3, 3, 3, Vehicle H_2O
Doses (mg/kg/sc) 12.0, 6.0, 3.0,

MCV 4143 substituted partially for morphine. Salivation, jaw sag, slowing and drowsiness were the main side effects noted at all three doses tested. Partial substitution does not necessarily imply morphine-like properties.

MCV 4144-NIH 9512-UM 1158. beta-(Aminomethyl)-p-chlorohydrocinnamic acid (Baclofen)



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 1.0, 10.0 and 30.0

2) TF vs M-0.06 (0.02-0.17)

3) PPQ-1.2 (0.4-3.4)

4) HP-2.1 (1.5-2.7)

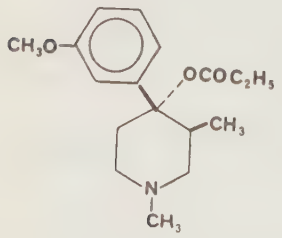
5) N-6/10 at 40.0 a toxic dose

MONKEY DATA (SDS)	# Animals				
	Doses(mg/kg/sc)	1 16.0	2 12.0	3 8.0	3 4.0

Vehicle;Dil HCl + H_2O

MCV 4144 did not substitute for morphine. At the highest dose, a convulsion was noted which was terminated with 30 mg of pentobarbital. The drug appeared to suppress the withdrawal signs retching and vomiting. Ataxia and uncoordination were noted. One monkey receiving 12 mg/kg fell asleep.

MCV 4146-NIH 9541-UM 1170. 4-beta-(m-Methoxyphenyl)-1,3-dimethyl-4-alpha-piperidinol propionate hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 1.0 and 10.0

2) TF vs M-Inactive at 1.0, 3.0 and 10.0

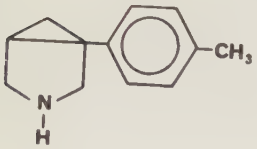
3) PPQ-18.7 (7.8-44.5)

4) HP-21.8 (14.6-32.7)

MONKEY DATA (SDS)	# Animals				
	Doses(mg/kg/sc)	3 16.0	3 8.0	3 4.0	Vehicle H_2O

At the highest dose tested, MCV 4146 appeared to substitute completely for morphine. Additional studies are recommended.

MCV 4147-NIH 9542. 1-(4-Methylphenyl)-3-azabicyclo-[3.1.0] hexane hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-30.9 (13.2-72.2)

2) TF vs M-Inactive at 10.0, 30.0 and 80.0

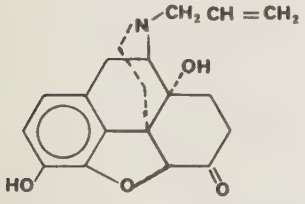
3) PPQ-4.8 (1.6-13.8)

4) HP-8/10 at 32.0; 0/8 at 24.0, 16.0 and 8.0. Toxic

MONKEY DATA (SDS) # Animals Doses(mg/kg/sc) 4 / 24.0, 4 / 12.0, 4 / 6.0; Vehicle H_2O

The drug substituted partially and very briefly for morphine soon after it was injected. Tremors and myoclonic spasms were prevalent especially at the 2 higher doses. In addition, salivation was seen in 2 animals at the highest dose. Partial substitution does not necessarily imply that a drug has morphine-like properties.

MCV 4152-NIH 9548. (+)-Naloxone hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-

2) TF vs M-

3) PPQ-

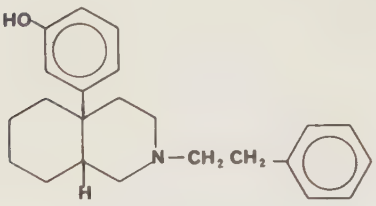
4) HP-

5) N-

MONKEY DATA (PPt-Withdrawal) # Animals Dose(mg/kg/sc), 2 / 5.0, Vehicle H_2O

This stereoisomer did not precipitate withdrawal signs at 5.0 mg/kg/sc whereas (-)-naloxone was active at 0.05 mg/kg/sc.

MCV 4154-NIH 9551. 10-m-Hydroxyphenyl-2-phenethyl-cis-deca-hydroisoquinoline



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-12.1 (4.1-35.6)

2) TF vs M-Inactive at 1.0, 10.1 and 30.0

3) PPQ-0.2 (0.1-1.0)

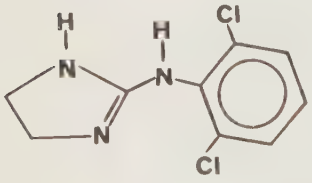
4) HP-3.2 (2.5-4.2)

MONKEY DATA (SDS)	# Animals				
Doses (mg/kg/sc)	2	3	3	1	
	60.0	48.0	24.0	12.0	

Vehicle Carboxymethylcellulose suspension

This drug did not substitute for morphine in the dose range tested. Drug supply was exhausted.

MCV 4155-MCV 4183-NIH 9549-NIH 9571. 2-(2,6-Dichloro-anilino)-2-imidazoline hydrochloride (Clonidine)



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-1.23 (0.23-6.65)

2) TF vs M-Inactive at 0.3, 1.0 and 30.0

3) PPQ-0.005 (0.001-0.02)

4) HP-1.0 (0.7-1.5)

MONKEY DATA A. (SDS)	# Animals					
Doses (mg/kg/sc)	3	3	3	6	6	6
	2.0	1.0	0.5	0.25	0.125	0.06

Vehicle H_2O

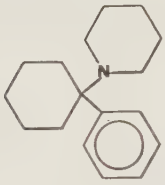
MCV 4155 substituted partially for morphine at all the doses tested. Drowsiness was a prominent sign noted at all doses. Ataxia was seen at the highest dose and slowing was observed at 1.0 mg/kg. Partial substitution does not necessarily imply that the drug has morphine-like properties.

B. (Primary Physical Dependence), Vehicle H_2O

Five non-dependent monkeys were given MCV 4155 (MCV 4183) at the doses indicated below sc every 6 hours. At the lowest dose (0.01 mg/kg), restlessness was noted. The dose was doubled on day 2

and restlessness was again noted. At 0.04 to 0.08 mg/kg, drowsiness, eyelid ptosis and slowing were seen. On day 8, the dose was raised to 0.1 mg/kg and by day 15 the dose was 0.25 mg/kg. The same signs noted for days 3-7 were consistently present during this period. The animals were placed in abrupt withdrawal on day 16 and fighting, yawning, and wet dogs developed. Later, a naloxone challenge (0.1 mg/kg/sc) was given and the same signs noted during abrupt withdrawal were again observed. The dose regimen was again increased to 3.0 mg/kg by day 30 and drowsiness, ptosis, and slowing were routinely observed, and occasionally fighting was seen. The animals were again placed in abrupt withdrawal on day 31, but no remarkable signs were seen. On days 32, 33 and 34 the dose was 6.6 mg/kg and drowsiness, fighting and tremors were recorded. On day 36, the dose was raised to 12.6 mg/kg and was raised to 14.4 the next day and dropped to 12.6 on day 38 because, in addition to the effects noted above, the animals stopped eating and were staring. The animals were placed in abrupt withdrawal on day 39. The only signs noted were residual drowsiness, fighting, avoiding contact, restlessness, wet dogs, scratching, and yawning. A naloxone challenge (1.0 mg/kg/sc) was without effect. Apparently, a high degree of tolerance but a very low degree of physical dependence developed with this agent. It does not appear to produce a significant degree of morphine-like physical dependence.

MCV 4158-NIH 9580. 1-(1-Phenylcyclohexyl)piperidine hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 1.0, 3.0 and 10.0

2) TF vs M-0,3 (0.1-1.0)

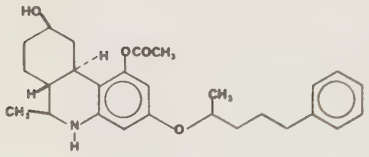
3) PPQ-1.4 (0.5-4.1)

4) HP-and N-(Not tested)

MONKEY DATA (SDS) # Animals Doses (mg/kg/sc) 3 / 0.2, 3 / 0.1, 3 / 0.05, Vehicle H_2O

This drug did not substitute for morphine. Severe dose-related ataxia and some body sag were seen. These effects lasted approximately 1 hour.

MCV 4161-NIH 9596. (-)-trans-5,6,6a,beta-7,8,9,10,10a alpha-octahydro-1-acetoxy-6-beta-methyl-3-(5-phenyl-2-pentyloxy)-phenanthridine hydrochloride



MOUSE DATA ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-1.7 (0.6-5.0)

2) TF vs M-Inactive at 3.0, 10.0 and 30.0

3) PPQ-0.1 (0.04-0.3)

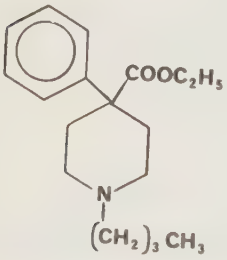
4) HP-0.15 (0.13-0.19)

MONKEY DATA (SDS)	# Animals Doses (mg/kg/sc)	3 / 0.5, 3 / 0.25, 3 / 0.125,

Vehicle Propylene Glycol-H_2O

This compound substituted partially for morphine at all doses tested. The signs of drowsiness and eyelid ptosis were noted in most of the animals, and slowing was seen in one monkey at each dose. Partial substitution does not necessarily imply that the compound has morphine-like properties.

MCV 4163-NIH 9599. N-n-Butylnormeperidine hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-27.5 (10.9-69.5)

2) TF vs M-Inactive at 3.0, 10.0 and 30.0

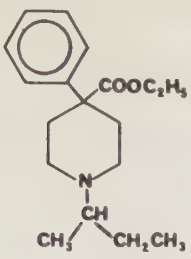
3) PPQ-7.5 (2.9-19.9)

4) HP-5.8 (4.2-8.0)

MONKEY DATA (SDS)	# Animals Doses (mg/kg/sc)	3 / 3.0, 3 / 1.5, 3 / 0.75, Vehicle H_2O

At the highest dose, MCV 4163 substituted completely and briefly (2 hours) for morphine.

MCV 4164-NIH 9600. N-sec-Butylnormeperidine hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-41.6 (16.5-105.4)

2) TF vs M-Inactive at 3.0 and 10.0

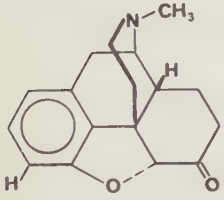
3) PPQ-7.5 (4.8-11.8)

4) HP-9.0 (6.8-12.0)

MONKEY DATA (SDS)	# Animals / Doses (mg/kg/sc)				Vehicle H_2O
	3 / 10.0	,	3 / 5.0	, 3 / 2.5	

MCV 4164 substituted partially for morphine at all three doses. At the highest dose, drowsiness, ataxia and salivation were noted. Partial substitution does not necessarily imply that the drug has morphine-like properties.

MCV 4165-NIH 9579. 3-Deoxydihydromorphinone hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-1.3 (0.46-3.9)

2) TF vs M -Inactive at 3.0, 10.0 and 30.0

3) PPQ-0.6 (0.2-1.8)

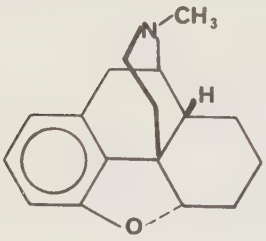
4) HP-0.6 (0.4-0.8)

5) N-0.9 (0.6-1.2)

MONKEY DATA (SDS)	# Animals / Doses (mg/kg/sc)				Vehicle H_2O
	3 / 3.0	,	3 / 1.5	, 3 / 0.75	

At the highest dose, MCV 4165 substituted completely and briefly (first 90 minutes) for morphine.

MCV 4166-NIH 9607. 3,6-Dideoxydihydromorphine hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-2.4 (0.9-6.6)

2) TF vs M -Inactive at 3.0, 10.0 and 30.0

3) PPQ-0.35 (0.14-0.85)

4) HP-0.37 (0.26-0.54)

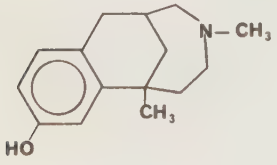
5) N-1.3 (1.1-1.5)

MONKEY DATA (SDS)	# Animals				
	Doses (mg/kg/sc)	2, 1.2	3, 0.6	3, 0.3	1, 0.15

Vehicle H_2O

At the highest dose, MCV 4166 substituted completely for morphine. The onset of action was prompt and the duration was approximately 1 1/2 hours. The duration of action of morphine is > 3 hours.

MCV 4167-NIH 9612. (±)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-6.4 (3.9-10.5)

2) TF vs M-19.8 (10.5-37.2)

3) PPQ-0.5 (0.2-1.3)

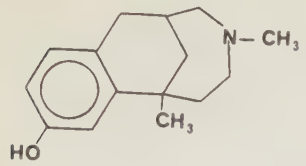
4) HP-0.40 (0.25-0.62)

MONKEY DATA (SDS)	# Animals				
	Doses (mg/kg/sc)	3, 12.0	2, 6.0	3, 3.0	

Vehicle Carboxymethylcellulose suspension

MCV 4167 did not substitute for morphine at the doses tested. Ataxia was noted at all doses and salivation was seen at the two higher doses.

MCV 4168-NIH 9613. (+)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-8.2 (3.1-21.8)

2) TF vs M -Inactive at 3.0, 6.0, 10.0 and 30.0

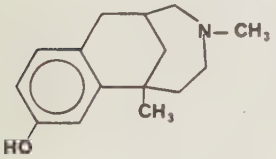
3) PPQ-0.9 (0.4-2.2)

4) HP-2.6 (2.1-3.4)

MONKEY DATA (SDS)	# Animals				
	Doses (mg/kg/sc)	3, 6.0	3, 3.0	3, 1.5	Vehicle H_2O

This compound did not substitute for morphine. At the highest dose, the drug appeared to exacerbate withdrawal. Ataxia was seen in all the animals receiving the highest dose and in 2 of 3 animals at the other doses. Tremors were also noted at the highest dose.

MCV 4169-NIH 9614. (-)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0 and 30.0

2) TF vs M-5.5 (1.2-25.9)

3) PPQ-0.4 (0.1-1.3)

4) HP-1.8 (1.3-2.4)

MONKEY DATA (SDS)	# Animals				
	Doses (mg/kg/sc)	3, 6.0	2, 3.0	3, 1.5	Vehicle H_2O

The compound did not substitute for morphine at the doses tested. The drug may have exacerbated withdrawal at the highest dose. In addition, ataxia was noted in all animals receiving this dose.

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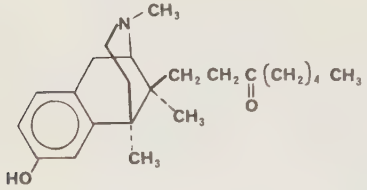
MCV 4175-NIH 9624. 1-[(2-alpha, 6-alpha, 11S)-(±)-1-(1,2,3,4,5, 6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-3-octanone methanesulfonate



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0 and 30.0
2) TF vs M-0.03 (0.81-0.07)
3) PPQ-0.2 (0.08-0.6)
4) HP-2.4 (1.7-3.3)

MONKEY DATA	# Animals				
A. (SDS)	Doses (mg/kg/sc)	3 / 0.5	3 / 0.25	3 / 0.125	Vehicle H_2O

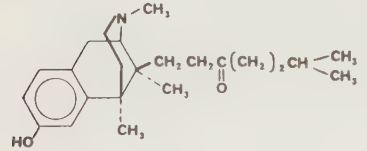
MCV 4175 did not substitute for morphine. At the highest dose, the drug appeared to exacerbate withdrawal. It was noted in the preliminary study that the animal spontaneously ejaculated semen frequently.

MONKEY DATA	# Animals				
B. (PPt-Withdrawal)	Doses (mg/kg/sc)	1 / 0.5	3 / 0.25	3 / 0.125	3 / 0.06

Vehicle H_2O

The drug promptly precipitated dose-related withdrawal signs. The duration of action was approximately twice that of naloxone. The male animals receiving MCV 4175 appeared to ejaculate semen spontaneously, much more frequently than either the positive control (naloxone) or vehicle control. One animal receiving the 0.25 dose ejaculated 14 times in 3 hours.

MCV 4176-NIH 9625. 1-[(2-alpha, 6 alpha, 11S)-(±)-1-(1,2,3,4,5, 6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methanol-3-benzazocin-11-yl)]-6-methyl-3-heptanone methanesulfonate



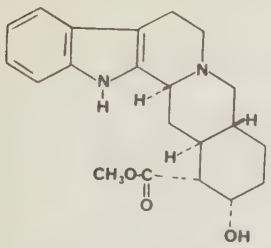
MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, 30.0 and 100.0
2) TF vs M-14.8 (3.7-58.6)
3) PPQ-0.002 (0.0003-0.016)
4) HP-1.1 (0.8-1.3)

MONKEY DATA	# Animals					
(SDS)	Doses (mg/kg/sc)	1 / 5.0	3 / 2.5	3 / 1.25	2 / 0.6	Vehicle H_2O

In the dose range tested, MCV 4176 did not substitute for morphine.

MCV 4184-NIH 9689. Yohimbine hydrochloride



MOUSE DATA- ED_{50} (95% C.L.)- (mg/kg/sc)

1) TF-Inactive at 3.0, 10.0 and 30.0

2) TF vs M-5.6 (2.7-11.5)

3) PPQ-17.1 (6.6 (44.1)

4) HP-(Not tested)

MONKEY DATA (SDS)	# Animals	2	3	3	1	Vehicle
	Doses (mg/kg/sc)	4.0	2.0	1.0	0.5	H_2O

Yohimbine did not substitute for morphine in the dose range tested. The drug appeared to exacerbate withdrawal during the first 1/2 hour. One monkey at each of 3 of 4 doses masturbated and ejaculated. At the 1.0 mg/kg, one monkey ejaculated spontaneously at least once per 1/2 hour observation period. None of the monkeys receiving vehicle displayed this behavior. Some jaw sag was also noted in the monkeys receiving yohimbine.

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Annual Report: Biological Testing Program of the Committee on Problems of Drug Dependence, Inc. (1979)

Jacobson, A. E.

About 140 compounds have been examined in my laboratory at NIH for any of several reasons over the past year. About a third of these were submitted to either the Medical College of Virginia (MCV) or to the University of Michigan (UM) for their examination. A considerable number of older drugs have been included in the UM/MCV reports in the 1979 Proceedings. These have not been published, heretofore. Sixteen of those reports are included in the UM folio for 1979, and one is in the MCV Addendum. Altogether, about 43 compounds are included in the 1979 Proceedings from UM. This is the same as, or perhaps slightly more than, the number of reports that UM printed in 1978. There are ca. 32 reports from the laboratories at MCV. There are several reasons for the difference in the numbers of reports from UM and MCV. The major difference lies in the number of older drugs reported by UM. When these are taken into consideration, we have about 30 reports on new drugs from each group. A substantial number of reports are being held on file in both units. These were not released for publication in 1979; we allow a submitter about three years before requiring release of data. Thus, about 120 compounds have been, or are being, examined and over 70 of these are in the 1979 Proceedings. Eventually, if submitters continue submitting and releasing data on compounds at the present rate, we could anticipate seeing ca. 30 reports on ca. 20 to 25 compounds per year from each group in the next few years.

About 60 percent of the compounds reported on by MCV/UM, and included in the 1979 Proceedings, have come from U.S. and foreign universities and from research institutions, including NIH; ca. 40 percent are from the pharmaceutical industry. This is at the low end of normal for industry. Generally, over the last few years, industrial submissions ranged between 40 and 60 percent. The published reports represent the work of about six industrial firms and the same number of universities and research

institutions: from one to nine submissions per independent group. It is difficult to tell, at this point, whether we are seeing the normal yearly fluctuation in interest in analgesic research, a sort of steady-state, or whether we have a slight decrease in interest. The next few years may allow us to determine that point. Certainly, however, we have not observed an increase in interest in the field of analgesics over the past year.

At this time when we see, at best, a steady-state interest in research on analgesics, the scientific involvement of the groups which cooperate with the Committee, that is, UM and MCV, has increased considerably. The scientific investigation of drugs received by the Committee is still weighted towards a study based on single-dose suppression, precipitated withdrawal and, occasionally, primary dependence experiments, in the rhesus monkey. However, at MCV, compounds are being examined by rat infusion techniques because there is reason to believe that some of these compounds act differently in different species. Further, all compounds, no matter where they are sent for the initial single-dose suppression (SDS) study, will be examined in rodent antinociceptive and antagonist assay systems at MCV (tail flick, tail flick antagonist and phenylquinone writhing [PPQ] tests), if the submitted sample is in sufficient supply. All samples will be examined biochemically for their binding affinity to the opiate receptor in rat brain homogenates, in electrically stimulated guinea pig ileum and in mouse vas deferens, at UM. Also, self-administration experiments with these drugs will be done more frequently, and reported in the Proceedings. Attempts will be made to correlate the results from these studies - to try to assign a drug to a previously known class, or to state differences from the known classes of drugs with various types of abuse potential.

Last year, the CPDD authorized joint meetings of involved personnel of UM and MCV at times other than the Annual Meeting. The meetings which the UM and MCV testing groups are holding to discuss their programs will result, in the near future, in the publication of a considerable amount of in vitro and in vivo data on analgesic compounds. These groups are now considering the way these data will be reported. It remains to be seen whether the increased data will help us predict whether a drug is likely to have dependence-producing properties of one sort or another. At the least, we will have obtained composite data on a reasonable number of compounds which will be most helpful to researchers in the field. I think that these joint UM/MCV meetings will be exceedingly valuable for the correlation of data on a drug, and for the solution of many other types of problems which are of common interest to these groups. One such problem which was discussed at the last joint meeting related to the FDA's recently promulgated Good Laboratory Practice (GLP) Regulations. The MCV and UM labs will work in compliance with the GLP. I am now requesting sufficient data from all submitters to allow these laboratories to remain in compliance with GLP regulations. Thus, all samples which are submitted through the CPDD will, henceforth,

either come with the necessary data, or they will not be accepted. Although the GLP regulations are an added burden to me and the UM and MCV laboratories, they can, it is hoped, serve to eliminate the examination of impure or improperly characterized compounds. Although this did not occur very often in the past, it did happen occasionally.

As can be noted from the UM and the MCV Annual Reports, we tested a considerable number of analogs of recognizable benzomorphans, piperidines, etc., for their abuse potential this year. Some of the benzomorphans and some of the morphinan-like compounds which were tested had unpredictable (a priori) properties.

Among the benzomorphans, we saw an antinociceptively weak N-ethyl compound which precipitated withdrawal (NIH 9258, MCV 4176). There were two N-methyl benzomorphans with very long side-chains at the C-9 beta position which, contrary to what would have been predicted, had essentially morphine-like antinociceptive activity and did not substitute for morphine in SDS (NIH 9624 and 9625, MCV 4175 and 4176 - the NIH 9624 precipitated withdrawal). Continuation of work, begun in 1978, with N-cyanoalkyl normetazocines and morphinans showed that they had narcotic antagonist properties in the monkey (NIH 9364A and 9369A, UM 1130A and 1133A - the NIH 9364A was 30 times more potent than morphine as an antinociceptive). NIH 9364A and its dextro enantiomer (NIH 9365B, UM 1131B) may prove biochemically useful. The levo compound has binding affinity for the opiate receptor 100,000 times that of its enantiomer. Enantiomeric differences of this magnitude have not been noted before. A number of racemic and enantiomeric C-homobenzomorphans (7-membered nitrogen-containing ring) were examined and found to be quite interesting. These were N-methyl compounds which did not have morphine-like properties in SDS (NIH 9612, 9613, 9614, 9560, 9561, 9562, 9563, 9564, and 9565; MCV 4167, 4168, 4169, UM 1174, 1175, 1176, 1177, 1178, and 1179, respectively). UM has found them to be biochemically intriguing compounds. It might be noted that I cannot explain why NIH 9612 (a racemic compound) is four times more potent in the hot plate assay than its levo enantiomer (NIH 9614).

Although ketobemidone-like compounds are not generally known for their narcotic antagonist activity (only a few have been observed to have antagonist activity, heretofore), three ketobemidones with antagonist activity were examined this year (NIH 9636, 9649 and 9650, UM 1191, 1197, 1198). Other types of substituted piperidines were also noted not to substitute for morphine in SDS (NIH 9559 and 9356, UM 1181 and 1147 - the NIH 9356 was meperidine-like in antinociceptive activity and had narcotic antagonist properties).

An unusual morphinan, substituted on the C-ring (NIH 9466, UM 1150 and MCV 4130), had potent narcotic antagonist activity, and a 6-oxamorphinan (NIH 9539, UM 1168) where the C-6 carbon atom in the C ring was replaced by oxygen, had four times the potency of

morphine as an antinociceptive, even in the hot plate assay, and had naloxone-like, long-lasting narcotic antagonist activity. Evidently, substituents on the C-ring of morphinans, unlike most substituents on the C-ring of morphine-like compounds, can be advantageous. The heteroatom replacement noted in NIH 9539 has not been attempted with morphine-like compounds, insofar as I am aware.

A structurally interesting opiate, without the phenolic hydroxyl group or the ally alcohol moiety of morphine, proved to be more potent than morphine as an antinociceptive. It substituted completely for morphine in SDS (NIH 9607, MCV 4166), and its binding affinity for the opiate receptor was about one-third that of morphine. Thus the phenolic hydroxyl group in morphine-like compounds does not appear to be essential for morphine-like antinociceptive activity, or for inducing physical dependence in monkeys.

A considerable number of compounds were examined which can only be classified under a "miscellaneous" heading. An acyclic tertiary amine on a cyclohexane ring, with an aromatic ring on the carbon alpha to the nitrogen atom (NIH 9468, MCV 4131 and UM 1152), was not morphine-like in SDS, but was codeine-like in the hot plate assay for antinociceptive activity. An isoindole (NIH 9506, UM 1155 and MCV 4140) appeared to be a potent long-acting antagonist, with little antinociceptive activity. The isoindole is a ring-contracted (and unsaturated) relative of decahydroisoquinoline, many of which have been examined in the last few years. Most such compounds (except for NIH 9551, MCV 4154) substitute for morphine in SDS. However, NIH 9551 is meperidine-like in actinociceptive activity and did not substitute for morphine. A phenanthridine (NIH 9513, UM 1159), with a structure reminiscent of THC, was a potent antinociceptive, and was not morphine-like in SDS. Its physical dependence capacity was rated as very low. This compound, which will be the subject of a paper at this meeting, was noted to cause dysphoria, confusion and catatonia in the monkey. An odd-looking amide (NIH 9470, MCV 4133), reminiscent of fentanyl, does not produce morphine-like physical dependence, nor is much tolerance developed to it. It has codeine-like antinociceptive activity.

Lastly, I would like to mention the work done on Baclofen (LIORESAL), NIH 9512, MCV 4144 and UM 1158), which has been stated to be a GABA-like inhibitor. In the Investigator Brochure on Baclofen, it was noted that the compound suppressed all of the abstinence signs in morphinized animals when administered one hour before naloxone administration (ca. 2.5mg/kg p.o.). A 20mg/kg p.o. dose blocked naloxone-precipitated symptoms. Baclofen was also noted to reduce the willingness of rats to self-administer morphine without reducing morphine's analgesic effect or tolerance to morphine. Thus, the compound was said to reduce physical dependence and to suppress drug-seeking behavior with doses which do not induce marked overt behavioral effects. These claims were brought to my attention by Dr. Heinz Sorer, at NIDA. Certainly,

if the claimed effects were duplicable in our laboratories, it would be of great interest to the Committee. Thus, the company most kindly provided us with a sufficient supply of NIH 9512, and the drug was examined at both MCV and UM. In the tail flick antagonist test it appeared to be a potent (naloxone-like) antagonist. In the hot plate assay it was noted to have about half of the potency of morphine; it was somewhat less potent in PPQ, and inactive in the tail flick assay. In monkeys, in SDS, it did not substitute for morphine. MCV noted that it appeared to block accessive withdrawal signs of retching and vomiting. At UM, at 8mg/kg, bizarre behavior was noted suggesting disorientation. Normal animals, with 8mg/kg of NIH 9512, exhibited incoordination and catatonia. Ataxia and incoordination were noted at MCV at 16mg/kg in morphinized animals, at which dose convulsions were observed. UM believed that the drug was not morphine-like, and had a very low estimated physical dependence capacity. I think that it would be of interest for UM and MCV, at their joint meeting, to attempt to relate their results to the notion that Baclofen reduces physical dependence and suppresses drug seeking behavior. Perhaps further work is needed with the compound.

In conclusion, if one looks closely at the compounds being prepared, it might be deduced that there is a trend towards moderately potent agonist-antagonist types (codeine-like antinociceptively). Admittedly, there would be a considerable market for these drugs. However, it is quite conceivable, if not likely, that the new "super aspirins" which are coming on the market may displace them. Neither the "super aspirins" nor the codeine-like agonist-antagonists will meet what I believe to be a major need for a potent analgesic for the treatment of severe chronic pain. More research is needed to find non-dependence producing compounds with morphine-like (or better) analgesic properties. Perhaps butorphanol or nalbuphine will help fill that gap. It is possible that some of the drugs which we have discussed, or their relatives, will be able to meet that need. From the biochemical viewpoint, a search is underway in several laboratories to find an antagonist for the kappa or, in Dr. Kosterlitz's nomenclature, delta receptor. Evidently, compounds like the prototypic ethylketocyclazocine cannot be effectively antagonized by naloxone. It is possible that UM, through its biochemical work with the receptor assays, will find such an antagonist among the compounds received under Committee auspices.

I would, once again, like to thank our colleagues at MCV and UM for the fine work which they have done under the auspices of the Committee. We are grateful to them.

AUTHOR

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Annual Report: Evaluation of New Compounds for Opioid Activity (1979)

Swain, H. H.; Woods, J. H.; Medzihradsky, F.; Smith, C. B.; Fly, C. L.

The flow of new compounds through the evaluation programs at The University of Michigan (UM) and the Medical College of Virginia (MCV) is coordinated by Dr. Arthur E. Jacobson, Medicinal Chemistry Section, NIAMDD, National Institutes of Health, Bethesda, MD. The drugs, which come originally from pharmaceutical companies, universities and government laboratories, are submitted to Dr. Jacobson, who performs the MOUSE ANALGESIA tests (see below).

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information, and (4) a recommended starting dose. Only after the evaluation is complete and the report submitted back to Dr. Jacobson are the chemical structure and the mouse analgesia data released to the evaluating laboratory.

In the present report, all the new data related to a particular drug are placed in a single location. Thus, the first eight compounds are those which have been studied in all four UM laboratories. Thereafter are presented several substances which have been evaluated by two techniques and finally those drugs which have been studied by a single method. Listed below are brief descriptions of the techniques which are employed in these several evaluations.

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

The single dose suppressions test (SDS) determines the ability of a drug to suppress the signs of abstinence in monkeys which have been made physically dependent by the chronic administration of morphine (3 mg/kg every six hours). Compounds suspected of having morphine-antagonist properties are tested for their ability to precipitate the abstinence syndrome in non-withdrawn (NW) morphine-dependent monkeys. Non-dependent monkeys (Normals) are used to determine whether the acute effects of the test drug are reversible by nalorphine or naloxone. In a primary addiction study (PAS) non-dependent monkeys receive the test drug every six hours for 30 days to determine whether abstinence signs will appear when the animals

are challenged with an antagonist or when drug administration is discontinued.

Details of these techniques have been presented in the ANNUAL REPORT to the Committee in 1963 (Minutes of the 25th Meeting).

SELF-ADMINISTRATION BY MONKEYS

The compounds were examined in monkeys which had been conditioned to self-inject codeine. Each of at least three monkeys was studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, directly observable changes in behavior were elicited by the compound.

The schedule of intravenous drug delivery was a fixed-ratio 30; when a light above a lever was illuminated, the 30th response in its presence turned off the fixed-ratio light and delivered a five-second intravenous drug injection in the presence of another light that was illuminated during drug delivery. After each injection, a ten-minute timeout condition was in effect during which responses had no programmed consequence and no lights were illuminated. Each of the two daily sessions consisted of 13 injections or 130 minutes, whichever occurred first. Other details of the procedure and initial findings of a variety of narcotics are given in a previous report (Woods, 1977, Committee Report, pages 420-437). Additional background material is available from Dr. Woods.

Doses of the drugs are described in terms of moles/kg/injection, to facilitate direct comparisons among drugs. Duplicate observations of codeine (7.5×10^{-5} mol/kg/injection; 0.32 mg/kg/injection) and of saline were obtained for each monkey. A saline substitution was conducted before and after the series of observations on a test drug; the rates of codeine-reinforced responding were obtained by a random sampling of two sessions interpolated between the drug-substitution sessions. These data are represented in the following graphs with individual symbols for each of the monkeys; in addition, using the same symbols, the mean of duplicate observations is given for the doses studied in each monkey. There are two additional types of averaged data presented. The closed circles indicate the averaged data for observations on the subset of monkeys used to study each drug under each of the experimental conditions. The open circles indicate the codeine and saline rates of responding of 20 monkeys studied under the same conditions. The brackets indicate $\pm$ 3 standard errors of the mean for codeine and + 3 standard errors of the mean for saline. In all cases, the rates of responding given are those calculated during the fixed-ratio portion of each session.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Details of the binding assay were described in the 1978 ANNUAL REPORT. Briefly, aliquots of a membrane preparation from rat

cerebrum were incubated with ^{3}H-etorphine in the absence and presence of 150 mM NaCl, and in the presence of different concentrations of a given opioid drug under investigation. Stereospecific, i.e., opioid-receptor related, binding of etorphine was determined and the inhibitory potency of the drugs was obtained from log-probit plots of the data. Values obtained with this membrane preparation for some representative opioid drugs are as follows:

DRUG	EC_{50} (nM)		
	+NaCl	-NaCl	+Na/-Na
Naltrexone	2.0	7.9	0.25
Naloxone	9.1	31.6	0.29
Nalorphine	20.0	51.3	0.39
Cyclazocine	3.6	6.4	0.56
Levallorphan	5.5	7.0	0.79
Dextrorphan	18400	14000	1.32
Levorphanol	21.4	15.4	1.39
Codeine	34700	17800	1.95
l-Pentazocine	174.0	85.1	2.04
d-Pentazocine	6190	8660	0.71
Morphine	142.0	60.2	2.36

NOTE: Binding data for an extensive number of compounds is included in the 1978 ANNUAL REPORT

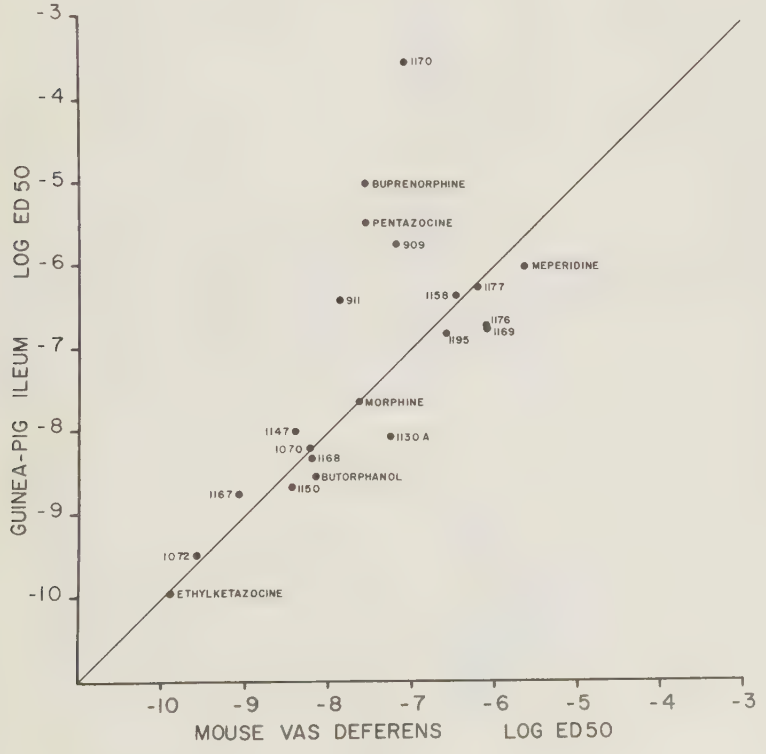
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA PIG ILEUM AND MOUSE VAS DEFERENS PREPARATIONS

Submitted drugs were evaluated on two smooth muscle preparations, the details of which were described in the 1978 ANNUAL REPORT. Shown on the following pages are the EC_{50}'s (± standard error) for the tested drug alone, for the drug in the presence of naltrexone (a pure opioid antagonist which is more effective against so-called "mu" agonists than against so-called "kappa" agonists), and for the tested drug in the presence of UM 979 (an antagonist which seems to be more effective against "kappa" than against "mu" drugs). The maximum depression (+ standard error) of the electrically induced twitch in each of these preparations is shown.

The type of opioid receptor upon which a drug acts has been inferred from the relative potencies of the drug in the mouse vas deferens and guinea-pig ileum preparations. Lord et al. (Nature 267: 495-499, 1977) have reported that kappa agonists such as ethylketazocine, UM 1070, UM 1072, UM 909 and UM 911 are more potent upon the guinea-pig ileum than upon the mouse vas deferens. The EC_{50}'s for a series of drugs upon the two preparations are shown

in the figure below. Drugs which were found to be equipotent upon the two preparations include kappa agonists such as ethylketazocine, UM 1070 and UM 1072, and mu agonists such as morphine. UM 909 and UM 911 were more potent upon the mouse vas deferens than upon the guinea pig ileum. Drugs with marked differences in their EC_{50}'s upon the two preparations included pentazocine and buprenorphine. The differences between the present findings and those of Lord et al. may be due to a difference in the strain of mouse which was used. Nevertheless, in the present studies the relative potencies upon the two preparations do not distinguish between the actions upon mu and kappa receptors.

By the use of appropriate antagonists it may be possible to differentiate between the two types of opioid receptors in the mouse van deferens (Smith, in Characteristics and Functions of Opioids eds. Van Ree and Terenius, Elsevier, North Holland Biomedical Press, p. 237-238, 1978). Drugs which are antagonized to a greater degree by UM 979 than by naltrexone appear to have more selectivity for the kappa receptor. Such drugs include UM 1070, UM 1072 and UM 911. It is interesting that meperidine, which has low potency upon both smooth muscle preparations, is not antagonized by either UM 979 or by naltrexone upon the mouse vas deferens. Other drugs which seem to be meperidine-like (e.g., UM1170) also are not blocked by either antagonist. Thus, antagonists seem to be useful for the classification of opiates.



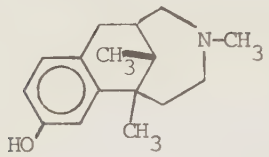
MOUSE ANALGESIA. Compounds were evaluated by Dr. Arthur Jacobson, who used the mouse hot-plate test and, in some cases, the Nilsen test. Below are reference values for these tests on several standard opioid drugs.

Compound	HOT PLATE [sc, mg/kg] / [sc, umol/kg]	HOT PLATE [oral, mg/kg] / [oral, umol/kg]	NILSEN [sc, mg/kg] / [sc,umol/kg]	NILSEN [oral, mg/kg] / [oral, umol/kg]
Morphine sulfate	1.0 (0.7-1.4) 3.0 (2.1-4.2)	6.3 (4.7-8.3) 18.9 (14.1-24.9)	0.7 (0.5-1.1) 2.1 (1.5-3.3)	8.3 (6.0-11.4) 24.9 (18.0-34.1)
Codeine phosphate	6.8 (4.5-10.2) 17.1 (11.3-25.7)	13.5 (9.7-18.7) 34.0 (24.4-47.1)	7.4 (4.9-11.0) 18.6 (12.3-27.7)	14.7 (9.2-23.3) 37.0 (23.2-58.7)
Levorphanol Tartrate	0.2 (0.1-0.3) 0.5 (0.2-0.7)	- -	0.2 (0.16-0.3) 0.5 (0.4-0.7)	2.5 (1.7-3.7) 6.2 (4.2-9.1)
Meperidine.HCl	4.6 (3.3-6.4) 16.2 (11.6-22.5)	- -	- -	- -
(-)-Metazocine.HBr	0.6 (0.5-0.9) 1.9 (1.4-2.8)	10.6 (8.0-14.1) 34.1 (25.7-45.3)	0.5 (0.3-0.7) 1.6 (1.0-2.3)	26.0 (21.0-33.0) 83.6 (67.5-106.1)
Dihydromorphinone.HCl	0.13 (0.11-0.16) 0.4 (0.3-0.5)	0.9 (0.7-1.2) 2.8 (2.2-3.7)	0.2 (0.15-0.3) 0.6 (0.5-0.9)	1.8 (1.5-2.1) 5.6 (4.7-6.5)

Nalorphine.HCl	9.9 (5.7-17.1)	-	23.0 (16.2-32.7)	-
	28.4 (16.4-49.1)	-	66.1 (46.6-94.0)	-
Cyclazocine	2.0 (1.4-2.8)	-	0.1 (0.07-0.16)	-
	7.4 (5.2-10.3)	-	0.4 (0.3-0.6)	-
Pentazocine	9.0 (6.5-12.4)	-	6.5 (4.4-8.8)	-
	31.6 (22.8-43.5)	-	22.8 (15.4-30.9)	-
Naltrexone.HCl	No dose response			
Naloxone.HCl	No dose response			

No antinociceptive activity in hot plate assay: Phenobarbital, amobarbital, valium, meprobamate, and mescaline.

Chlorpromazine.HCl	1.1 (0.9-1.5)
	3.2 (2.4-4.2)



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 1.2 (0.9-1.6)

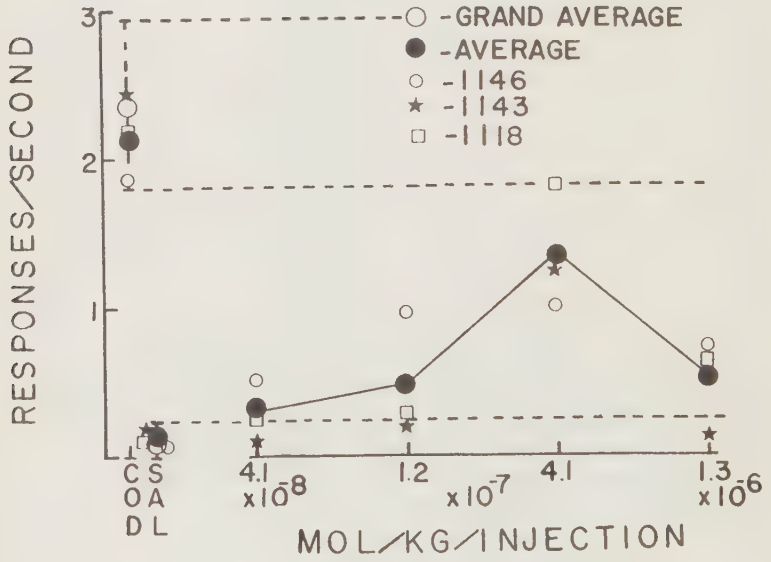
Nilsen: ---

dl-7,12 beta-Dimethyl-9-hydroxy-4-methyl-C-homobenzomorphan

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This drug so alters the behavior of the animals that abstinence signs cannot be graded accurately. It causes motor incoordination, apparent confusion and marked alteration in the animals' response to their environment. Doses tested: SDS, 0.6-2.4; normals, 2.4 mg/kg. Vehicle: water

SELF-ADMINISTRATION BY MONKEYS



UM 1177

UM 1177 maintained rates of self-administration slightly below the control rates for codeine. In this respect, the compound resembles a variety of other morphine-like drugs. It is comparable to codeine in potency.

UM 1177 NIH 9563 (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-NA	+Na/-Na
EC_{50} (nM)	1381	632	2.18

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC_{50}	Maximum Depression
Drug alone	5.54 (±0.45) x 10^{-7}M	55.12 (±2.56)%
After naltrexone, 10^{-7}M	(No response to any dose of UM 1177)	
After UM 979, 10^{-7}M	(No response to any dose of UM 1177)	

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC_{50}	Maximum Depression
Drug alone	6.22 (±0.84) x 10^{-7}M	84.04 (±2.29)%
After naltrexone, 10^{-8}M	5.24 (±0.99) x 10^{-7}M	82.10 (±4.75)%
After UM 979, 10^{-8}M	4.67 (±1.20) x 10^{-7}M	70.28 (±4.88)%

SUMMARY:

This compound is not a typical opioid:

It so alters the behavior of the monkeys (motor incoordination, apparent confusion and marked alteration in the animals' response to their environment) that abstinence signs cannot be graded accurately

The drug is self-administered by monkeys

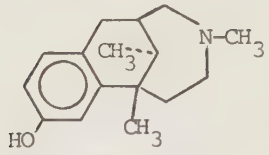
It competes for etorphine binding sites with a morphine-like sodium ratio but a very low potency

In the mouse vas deferens preparation, it depresses the electrically driven twitch, but it is far less potent and somewhat less effective than morphine and its actions are not blocked by naltrexone or UM 979

In the guinea-pig ileum preparation, the drug has a biphasic action: in low doses it depresses the electrically induced twitch somewhat, but at higher doses it enhances the twitch without altering the resting tension of the preparation

In the mouse hot-plate test, UM 1177 is a moderately potent analgesic

314-300 O -80 - 25



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 1.3 (1.0-1.7)

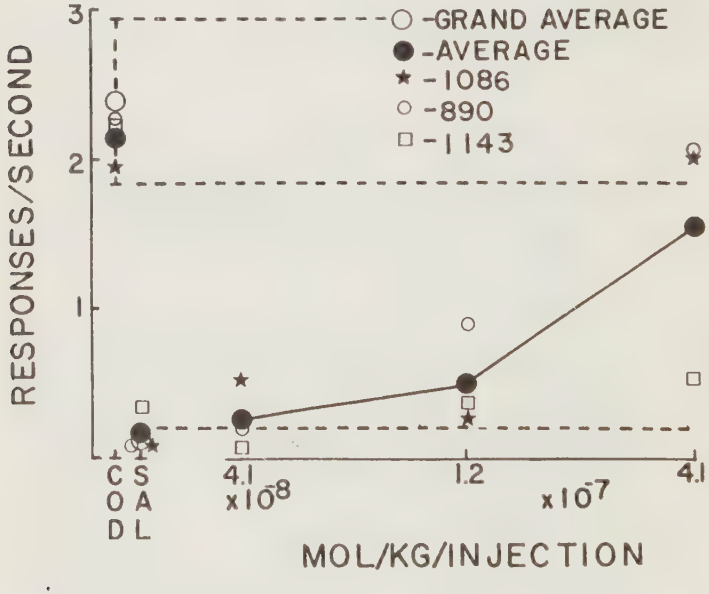
Nilsen: ---

(-)-7,12 alpha-Dimethyl-9-hydroxy-4-methyl-C-homobenzomorphan

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

Apparently this drug does not suppress or precipitate morphine abstinence signs. It so alters the behavior of the monkeys, with prominent confusion and ataxia, that it is not possible to grade the abstinence signs accurately. Doses tested: SDS, 0.7-5.6; normals, 5.6 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS



UM 1176

UM 1176 was self-injected by two of three monkeys at rates comparable to those of codeine; it was comparable to codeine in potency. Higher doses were not evaluated due to solubility problems.

UM 1176 NIH 9562 (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	453.1	245.5	1.85

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC_{50}	Maximum Depression
Drug alone	1.86 ($\pm$0.22) x 10^{-7}M	29.13 ($\pm$3.17)%
After naltrexone, 10^{-7}M	(No response to any dose of UM 1176)	
After UM 979, 10^{-7}M	(No response to any dose of UM 1176)	

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC_{50}	Maximum Depression
Drug alone	7.97 ($\pm$0.74) x 10^{-7}M	81.97 ($\pm$2.91)%
After naltrexone, 10^{-8}M	1.72 ($\pm$0.34) x 10^{-6}M	78.02 ($\pm$4.93)%
After UM 979, 10^{-8}M	3.22 ($\pm$1.38) x 10^{-6}M	68.55 ($\pm$3.37)%

SUMMARY:

This compound is not a typical opioid:

Apparently it does not affect the signs of morphine abstinence, but it causes so much atypical behavior (motor incoordination, apprehension, apparent confusion) that it is not possible to grade abstinence signs accurately

It competes for etorphine binding sites with a morphine-like sodium ratio and low potency

In depressing the twitch in the mouse vas deferens preparation, it is far less potent and somewhat less effective than morphine and its actions are not blocked by naltrexone or UM 979

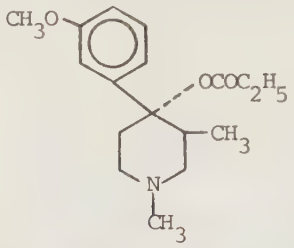
In the guinea-pig ileum preparation, the drug has a biphasic action: in low doses it depresses the electrically induced twitch somewhat, but at higher doses it enhances the twitch without altering the resting tension

The drug is self-administered by monkeys

It is a moderately potent analgesic in the mouse hot-plate test

UM 1176 differs structurally from UM 1177 in that the methyl group in the 12-position is alpha instead of beta in configuration, and is the l isomer.

UM 1170 NIH 9541 MCV 4146



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 21.8 (14.6-32.7)

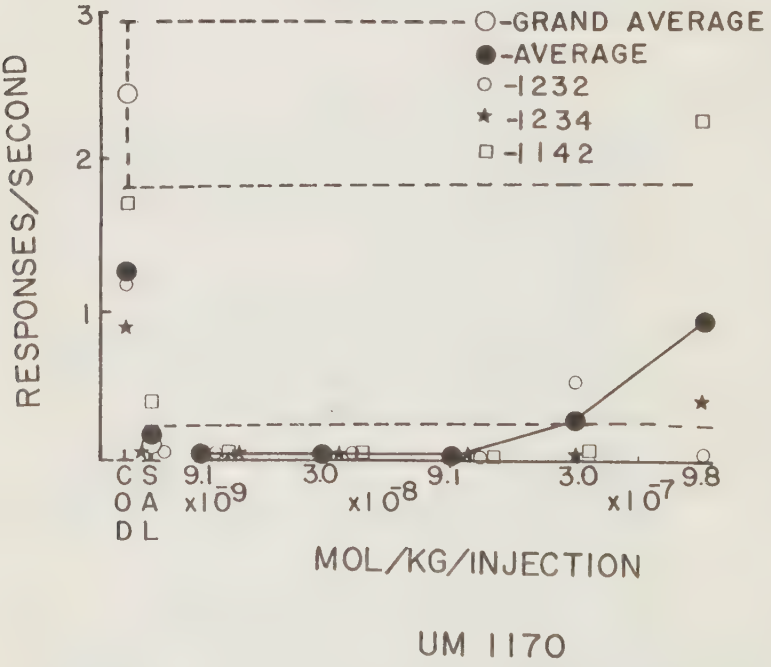
Nilsen: ---

4 beta-(m-Methoxyphenyl)-1,3-dimethyl-4 alpha-piperidinol propionate hydrochloride

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This is an opioid agonist, less potent than morphine and somewhat shorter acting. Doses tested: SDS, 5.0-20.0 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS



UM 1170 was self-injected at rates comparable to codeine in one of three monkeys at the highest dose. Higher doses of the drug were not evaluated due to inadequate drug supply.

UM 1170 NIH 9541 MCV 4146 (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	>2000	>2000	---

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC_{50}	Maximum Depression
Drug alone	3.08 (±1.72) x 10^{-4}M	90.90 (±4.60)%
After naltrexone, 10^{-7}M	1.89 (±0.51) x 10^{-4}M	91.63 (±5.01)%
After UM 979, 10^{-7}M	3.70 (±0.16) x 10^{-4}M	88.89 (±11.1)%

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC_{50}	Maximum Depression
Drug alone	7.78 (±4.06) x 10^{-8}M	38.61 (±2.63)%
After naltrexone, 10^{-8}M	1.54 (±0.55) x 10^{-8}M	25.05 (±1.49)%
After UM 979, 10^{-8}M	5.94 (±1.93) x 10^{-8}M	35.54 (±3.52)%

SUMMARY:

This drug seems to be an opioid of low potency:

To suppress the signs of morphine abstinence, a dose of 20 mg/kg is required

Data are insufficient to determine whether or not doses above 1 mg/kg are self-administered; lower doses are not

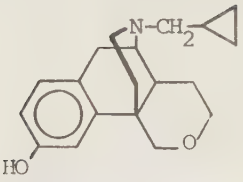
If it competes for etorphine binding sites, the EC_{50} is greater than 2000 nM

In the mouse hot-plate test, it has analgetic activity but the ED_{50} is 21.8 mg/kg

It depresses the electrically induced twitch in the guinea-pig ileum preparation but only at the enormous concentration of 10^{-4}M, and this action is not antagonized by naltrexone or UM 979

Only on the mouse vas deferens preparation does this drug have a potency approaching that of morphine, and the effect on this tissue is not blocked by naltrexone or UM 979.

UM 1168 NIH 9539



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.32 (0.25-0.42)

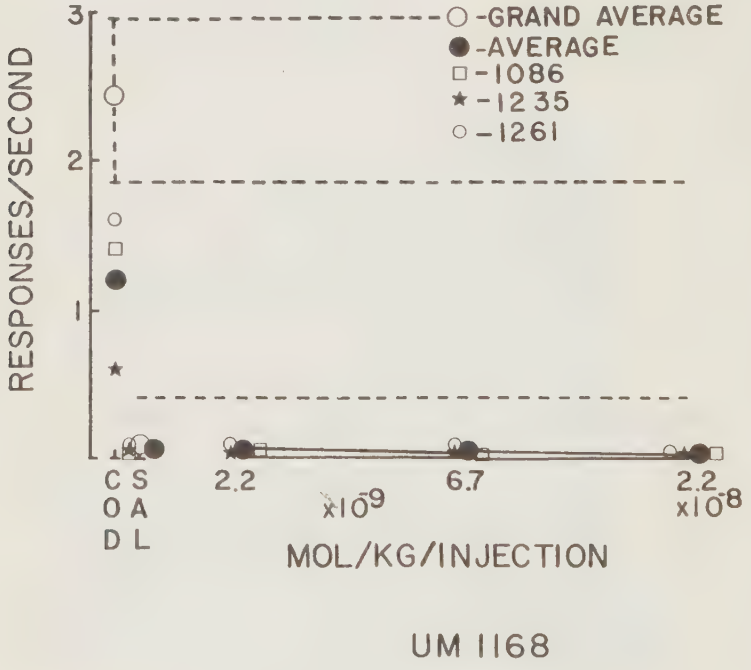
Nilsen: ---

17-Cyclopropylmethyl-3-hydroxy-6-oxamorphinan tartrate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This drug is an opioid antagonist, approximately equal in potency to, but longer lasting than, naloxone. Doses tested: SDS, 0.2; NW, 0.05-0.4 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS



UM 1168, at none of the doses tested, maintained self-injection at rates above those seen with saline.

UM 1168 NIH 9539 (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	1.03	0.972	1.06

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC_{50}	Maximum Depression
Drug alone	4.83 (±2.28) x 10^{-9}M	19.29 (±5.38)%
After naltrexone, 10^{-9}M	3.47 (±1.08) x 10^{-8}M	52.91 (±6.28)%
After UM 979, 10^{-7}M	9.20 (±2.18) x 10^{-9}M	45.28 (±4.27)%

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC_{50}	Maximum Depression
Drug alone	6.28 (±1.29) x 10^{-9}M	88.38 (±1.97)%
After naltrexone, 10^{-8}M	8.27 (±1.68) x 10^{-9}M	91.36 (±1.62)%
After UM 979, 10^{-8}M	6.53 (±1.19) x 10^{-9}M	91.06 (±1.68)%

SUMMARY

This compound behaves like many other opioid antagonists in that:

It precipitates the abstinence syndrome in the morphine-dependent monkey

Naltrexone and UM 979 do not greatly antagonize its twitch-depressant actions in the guinea-pig ileum and mouse vas deferens preparations

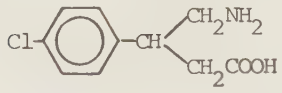
It is not self-administered by monkeys

It has a high affinity and an intermediate sodium-response ratio in competing with etorphine for binding sites

Nevertheless:

Unlike naloxone and naltrexone, it is a potent analgesic in the mouse hot-plate test

UM 1158 NIH 9512 MCV 4144 Baclofen



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 2.1 (1.5-2.7)

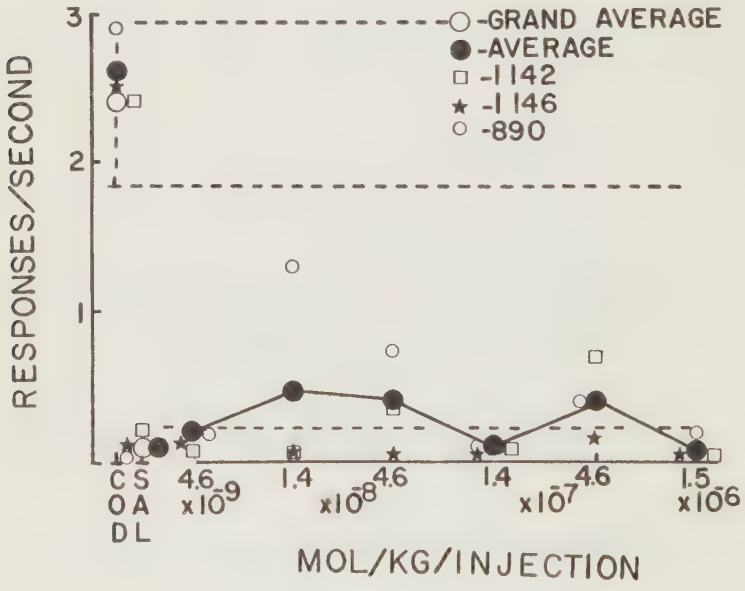
Nilsen: Six out of seven were affected at 40 mg/kg, a toxic dose

beta-Aminomethyl-p-chlorohydrocinnamic acid

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This compound causes an atypical CNS depression with bizarre uncoordinated behavior and a catatonic appearance. These effects were not reversed by the administration of nalorphine or of naloxone. Doses tested: SDS, 1.0-8.0; NW, 1.0; normals, 8.0 mg/kg. Vehicle: dilute hydrochloric acid.

SELF-ADMINISTRATION BY MONKEYS



UM 1158

UM 1158 maintained response rates above saline but well below codeine in two of the three monkeys tested, and in only one of these two monkeys, and only at one dose, did the rate exceed one response per second. This is the first compound to be tested as an unknown after it had been studied as a known drug (see 1978 Annual Report, p. 658). Results of the two studies are comparable.

UM 1158 NIH 9512 MCV 4144 Baclofen (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	>2000	>2000	---

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC_{50}	Maximum Depression
Drug alone	4.47 (±1.26) x 10^{-7}M	38.77 (±4.03)%
After naltrexone, 10^{-7}M	2.10 (±1.09) x 10^{-5}M	28.94 (±10.9)%
After UM 979, 10^{-7}M	1.38 (±0.43) x 10^{-6}M	43.78 (±6.72)%

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVE MOUSE VAS DEFERENS

	EC_{50}	Maximum Depression
Drug alone	3.37 (±1.98) x 10^{-7}M	69.02 (±2.14)%
After naltrexone, 10^{-8}M	5.34 (±2.25) x 10^{-7}M	61.83 (±4.74)%
After UM 979, 10^{-8}M	7.34 (±6.59) x 10^{-6}M	58.78 (±8.78)%

SUMMARY

This compound is neither an opioid agonist nor an opioid antagonist:

- It neither suppresses nor precipitates morphine abstinence signs in the monkey
- Its direct effects in the monkey are not reversed by nalorphine or naloxone
- It does not compete effectively for etorphine binding sites

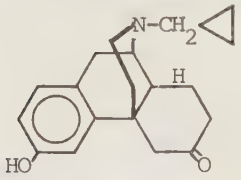
Nevertheless:

- UM 1158 is a potent analgesic in the mouse hot-plate test
- It causes atypical behavior in monkeys (incoordination, catatonia, apparent disorientation)
- Generally, it is not self-administered by monkeys

Interestingly:

- On the guinea-pig ileum preparation, the EC_{50} of this drug was increased 50-fold by naltrexone, while on the mouse vas deferens the EC_{50} was increased 20 times by UM 979

UM 1150 NIH 9466 MCV 4130



MOUSE ANALGESIA, ED_{50} (mg/kg)

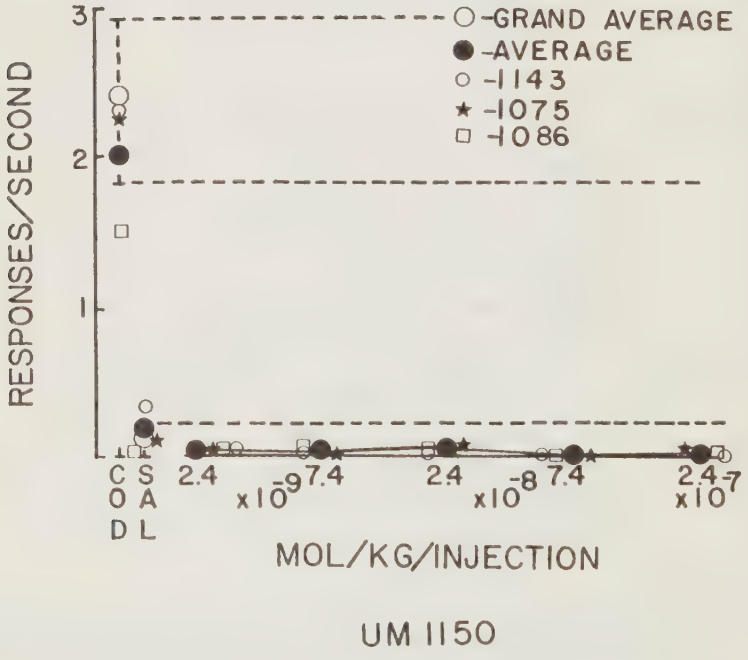
Hot Plate: 17.2 (13.3-22.2)
(Poor dose-response at higher dose levels)

(-)-17-(Cyclopropylmethyl)-3-hydroxymorphinan-6-one methanesulfonate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This drug is a potent antagonist which precipitates long-lasting abstinence signs in the dependent monkey. In normal animals it produced CNS depression which is antagonized by naloxone but potentiated by nalorphine. Doses tested: SDS, 0.5; NW, 0.0625-0.5; normals, 0.5 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS



As shown above, none of the doses of UM 1150 maintained response rates above those of saline.

UM 1150 NIH 9466 MCV 4130 (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	0.475	0.945	0.50

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC_{50}	Maximum Depression
Drug alone	3.54 (±0.56) x 10^{-9}M	72.24 (±2.84)%
After naltrexone, 10^{-7}M	5.69 (±1.25) x 10^{-9}M	73.96 (±1.18)%
After UM 979, 10^{-7}M	3.39 (±0.26) x 10^{-9}M	69.11 (±4.38)%

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

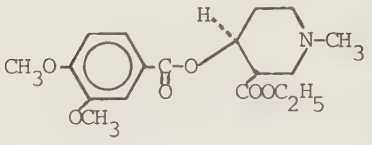
	EC_{50}	Maximum Depression
Drug alone	2.04 (±0.60) x 10^{-9}M	28.11 (±2.51)%
After naltrexone, 10^{-8}M	1.19 (±0.40) x 10^{-8}M	40.63 (±3.67)%
After UM 979, 10^{-8}M	5.35 (±1.68) x 10^{-9}M	32.53 (±7.28)%

SUMMARY

This compound is similar to nalorphine in many respects:

- It precipitates the signs of abstinence in morphine-dependent monkeys
- It is not self-administered by monkeys
- It has a high affinity and a low sodium-response ratio in competing with etorphine for binding sites
- It has analgetic activity in the mouse hot-plate test
- In normal monkeys it produces CNS depression which is antagonized by naloxone
- On the mouse vas deferens preparation, the EC_{50} is increased significantly by naltrexone

This compound is remarkable for its long duration of action in the monkey (40 hours) and for its high affinity for the etorphine binding site (EC_{50} of 0.475 in the presence of sodium)



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 4.0 (2.4-6.7)

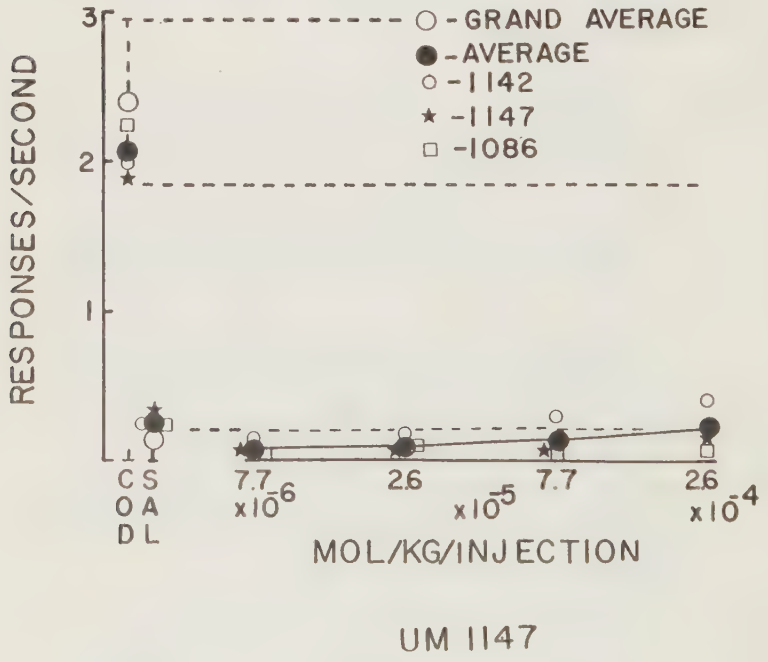
Nilsen: Six out of eight affected at 20 mg/kg (toxic); zero out of eight at 10 mg/kg

cis-3-Carbethoxy-4-hydroxy-1-methylpiperidine 4-(3,4-dimethoxybenzoate) hydrochloride

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This opioid antagonist is less potent but longer acting than nalorphine. Higher doses cause convulsions. In non-dependent monkeys it causes mild CNS depression which is antagonized by nalorphine and by naloxone. Doses tested: SDS, 2.0-4.0; NW, 2.0-8.0; normals, 4.0 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS



UM 1147

None of the tested doses of UM 1147 maintained rates of responding above those of saline.

UM 1147 NIH 9356 (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	>2000	>2000	---

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

Only concentrations of 10^{-8} and 3×10^{-8}M of UM 1147 depressed the twitch, and then only to the extent of 18 per cent. At concentrations between 10^{-7} and 3×10^{-5}M, the drug caused contraction (baseline shift), with an EC_{50} of $1.15 (\pm 0.45) \times 10^{-5}$M. The maximum contraction was 74.40 (±6.16)% of that produced by a maximally effective concentration of carbachol (10^{-5}M). In the presence of UM 1147 (10^{-7}M), the EC_{50} for morphine to depress the twitch was $5.86 (\pm 1.93) \times 10^{-8}$M; for morphine alone, the EC_{50} in this preparation was $3.41 (\pm 1.03) \times 10^{-8}$M.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC_{50}	Maximum Depression
Drug alone	$4.12 (\pm 0.76) \times 10^{-9}$M	88.64 (±2.71)%
After naltrexone, 10^{-8}M	$8.68 (\pm 2.88) \times 10^{-9}$M	86.15 (±4.88)%
After UM 979, 10^{-8}M	$4.18 (\pm 0.20) \times 10^{-9}$M	90.56 (±3.21)%

SUMMARY

In some ways, UM 1147 seems to belong to the opioid family of drugs and in some ways it does not. For instance:

- In non-withdrawn, morphine-dependent monkeys, it precipitates what appears to be a typical abstinence syndrome, and it intensifies the abstinence signs in withdrawing, dependent monkeys
- In normal monkeys it produces CNS depression which is antagonized by nalorphine and naloxone

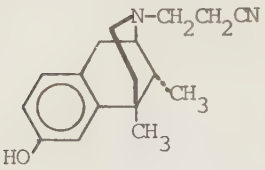
On the other hand:

- UM 1147 does not compete effectively for the etorphine binding site
- On the guinea-pig ileum, a large dose (10^{-7}M) failed to antagonize the actions of morphine

Miscellaneously:

- UM 1147 is not self-administered by rhesus monkeys
- It is a moderately potent analgesic in the mouse hot-plate test
- In the guinea-pig ileum preparation, it causes a contraction, similar to that seen with the "abstinence-producing compounds", UM 1037 and UM 1046

UM 1130A NIH 9364A



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.04 (0.03-0.05)

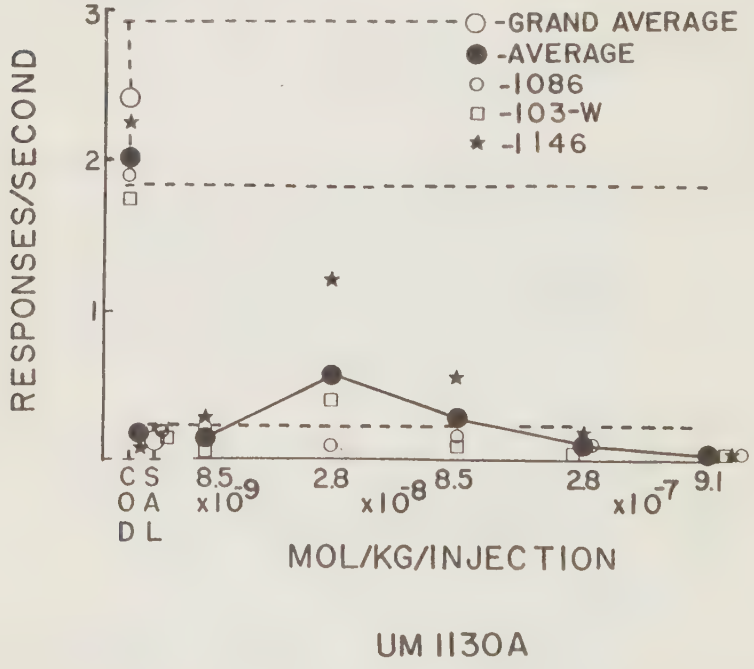
Nilsen: 0.01 (0.008-0.017)

(-)-2-(2-Cyanoethyl)-5,9 alpha-dimethyl-2'-hydroxy-6,7-benzomorphan hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This unusual compound precipitates abstinence signs in the non-withdrawn, morphine-dependent animal but does not make abstinence more severe in the withdrawn monkeys. In the latter animals, it causes ataxia, tremors and stupor. Doses tested: SDS, 0.16-2.56; NW, 0.32-1.28 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS



UM 1130A

UM 1130A maintained self-injection responding in only one of three monkeys tested with the compound. At no dose did the drug maintain response rates comparable to those with codeine.

UM 1130A NIH 9364A (continued)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	34.8	22.7	1.53

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

	EC_{50}	Maximum Depression
Drug alone	8.55 (±1.06) x 10^{-9}M	42.28 (±7.41)%
After naltrexone, 10^{-7}M	7.45 (±1.57) x 10^{-8}M	54.02 (±8.75)%
After UM 979, 10^{-7}M	1.07 (±0.03) x 10^{-7}M	46.91 (±6.55)

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC_{50}	Maximum Depression
Drug alone	5.47 (±0.82) x 10^{-8}M	100.0 (±0.00)%
After naltrexone, 10^{-8}M	1.41 (±0.42) x 10^{-7}M	96.60 (±1.70)%
After UM 979, 10^{-8}M	5.50 (±1.45) x 10^{-8}M	100.0 (±0.00)%

SUMMARY

Opioid agonist activity is suggested by several observations:

UM 1130A is a potent analgesic in the mouse hot-plate test

Naltrexone antagonizes its depressant effect upon the guinea-pig ileum and mouse vas deferens preparations, and UM 979 antagonizes its effects on the guinea pig ileum

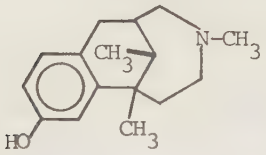
It competes for etorphine binding sites with a moderately high affinity and sodium ratio

In the monkey it causes mydriasis, ataxia and stupor

However:

It does not suppress the signs of morphine abstinence in the monkey; in fact, it precipitates abstinence signs in dependent animals

It has little if any tendency for self-administration



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.57 (0.42-0.78)

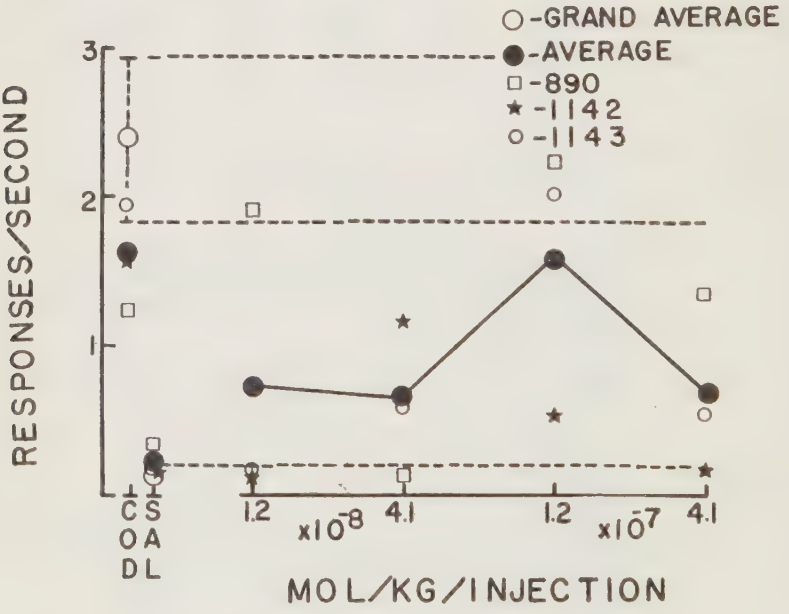
Nilsen: ---

(-)-7,12 beta-Dimethyl-9-hydroxy-4-methyl-C-homobenzomorphan

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

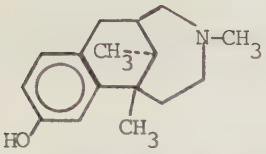
This drug causes such marked motor incoordination and apparent confusion that the signs of morphine abstinence cannot be evaluated. There is no evidence that it suppresses abstinence, although one cannot be sure. Doses tested: SDS, 0.3-2.4; normals, 2.4 mg/kg. Vehicle: 2/3 ethanol; 1/3 Emulphor EL 620.

SELF-ADMINISTRATION BY MONKEYS



UM 1179

UM 1179 maintained rates of responding comparable to codeine in two of the three monkeys; the third monkey showed maximal rates of responding that were slightly below those of codeine. These lower rates were obtained at a lower dose.



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 8.2 (5.4-12.4)

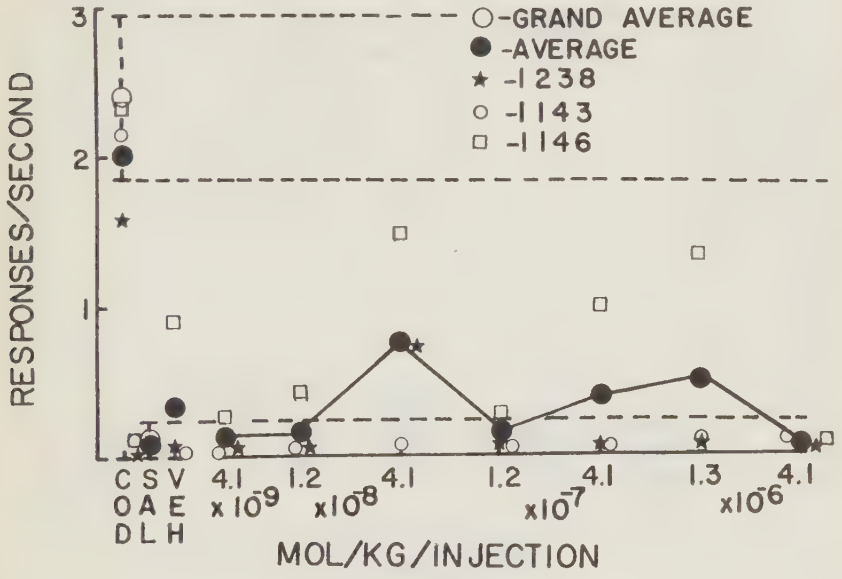
Nilsen: ---

(+)-7,12 alpha-Dimethyl-9-hydroxy-4-methyl-C-homobenzomorphan

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This drug causes marked alteration in the behavior of the monkeys, in that they show marked muscle incoordination, fail to behave normally to handling and appear to be confused. The drug neither suppresses nor precipitates the abstinence syndrome in these morphine-dependent monkeys. Doses tested: SDS, 0.5-4.0 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS

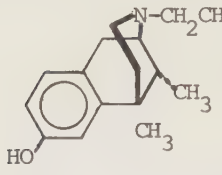


UM 1175

Self-injection rates of responding in one of three monkeys (#1146) were higher for the vehicle (Emulphor plus ethanol) than for saline. When this is taken into account, UM 1175 maintained self-injection behavior at no dose comparable to codeine. The single dose of 4.1 x 10^{-8} M/kg/injection may have maintained minimal self-injection responding.

314-300 O -80 - 26

UM 1131B NIH 9365B



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: No dose-response
(One out of ten affected at 100 mg/kg)

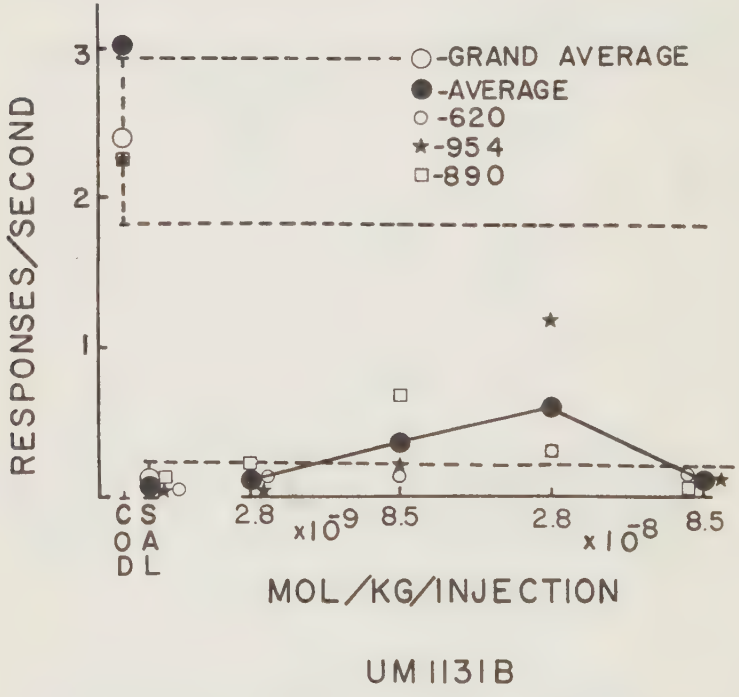
Nilsen: ---

(+)-2-(2-Cyanoethyl)-5,9 alpha-dimethyl-2'-hydroxy-6,7-benzomorphan hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

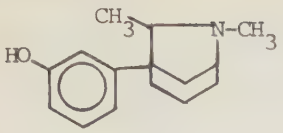
In the doses tested, the drug had only minimal CNS depressant effects. The supply of drug is depleted, so higher doses could not be tested. Doses tested: SDS, 1.5-12.0 mg/kg.

SELF-ADMINISTRATION BY MONKEYS



UM 1131B maintained self-injection rates slightly above those for saline at one dose in two of the three monkeys exposed to it.

UM 998 NIH 8877



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 8.0 (6.2-10.2)

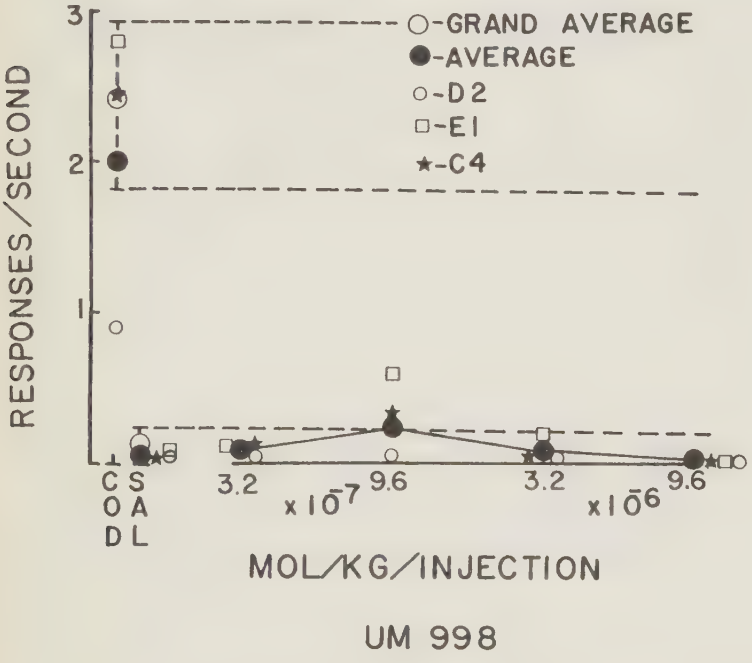
Nilsen: 3.4 (2.1-5.6)

(+)-1-m-Hydroxyphenyl-6,7-dimethyl-6-azabicyclo [3,2,1] octane hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

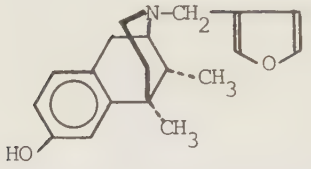
This drug is a morphine antagonist, significantly less potent than nalorphine. Doses tested: SDS, 1.0; NW, 1.0-8.0 mg/kg. Vehicle: water. Previously described in the 1975 ANNUAL REPORT.

SELF-ADMINISTRATION BY MONKEYS



At no tested dose was UM 998 self-injected at rates exceeding those for saline.

UM 979 NIH 8859 Mr-1452-MS



MOUSE ANALGESIA, ED_{50}, (mg/kg)

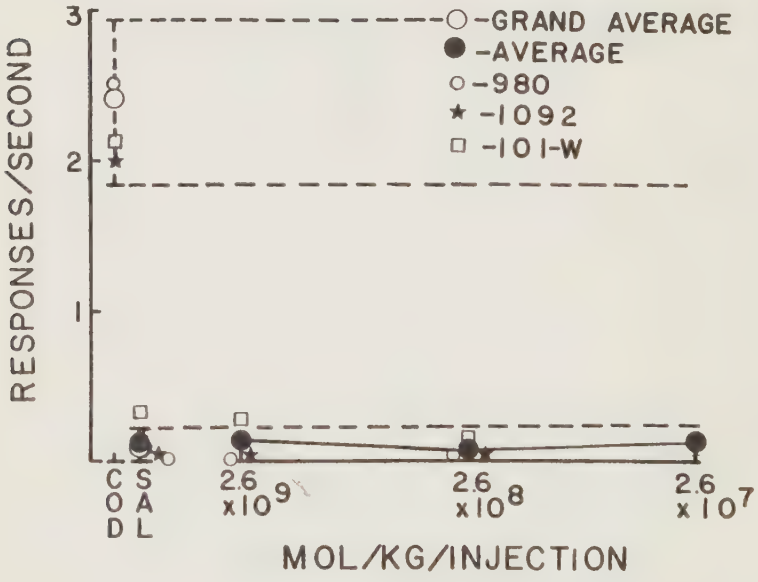
Hot Plate: Inactive to 100 mg/kg, a toxic dose.

(-)-5,9 alpha-Dimethyl-2-(3-furylmethyl)-2'-hydroxy-6,7-benzomorphan methanesulfonate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This is a potent narcotic antagonist with a very steep dose-response curve. Doses tested: SDS, 0.1; NW, 0.025-0.10 mg/kg. Vehicle: water. Previously described in the 1974 ANNUAL REPORT.

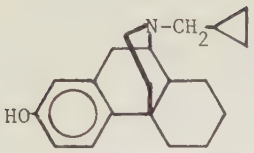
SELF-ADMINISTRATION BY MONKEYS



UM 979

UM 979 does not maintain responding at rates greater than saline in any dose tested.

UM 921 NIH 8747



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 4.4 (3.4-5.8)

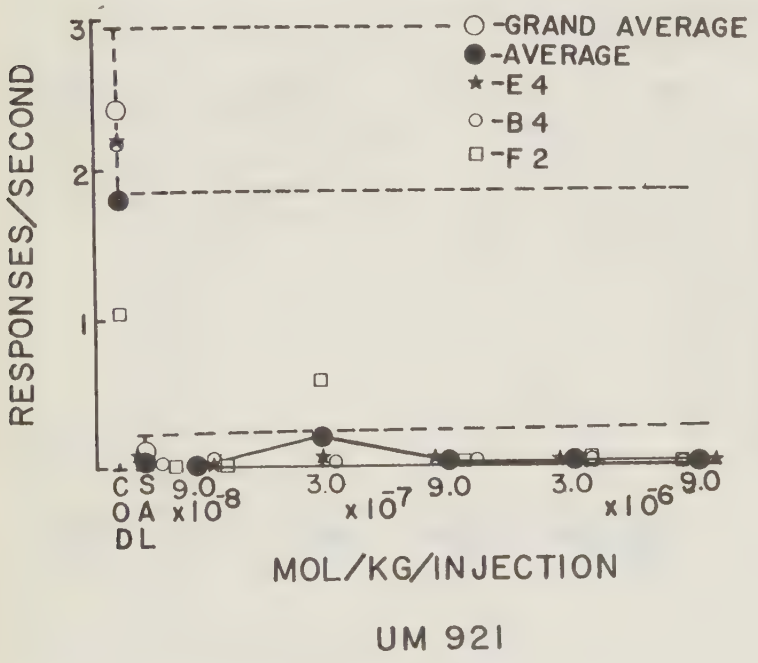
Nilsen: 1.2 (0.83-1.64)

(-)-N-Cyclopropylmethyl-2-hydroxymorphinan hydrochloride

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

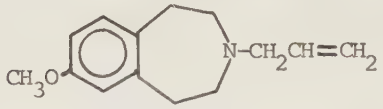
This drug is a long-acting morphine antagonist which shows more depression and ataxia than does nalorphine. Doses tested: SDS, 4.0; NW, 2.0-16.0 mg/kg. Vehicle: water. Previously described in the 1974 ANNUAL REPORT.

SELF-ADMINISTRATION BY MONKEYS



Only one dose in one monkey produced responding at a rate greater than saline.

UM 729 NIH 8310 and NIH 8377



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: Inactive to 100 mg/kg.

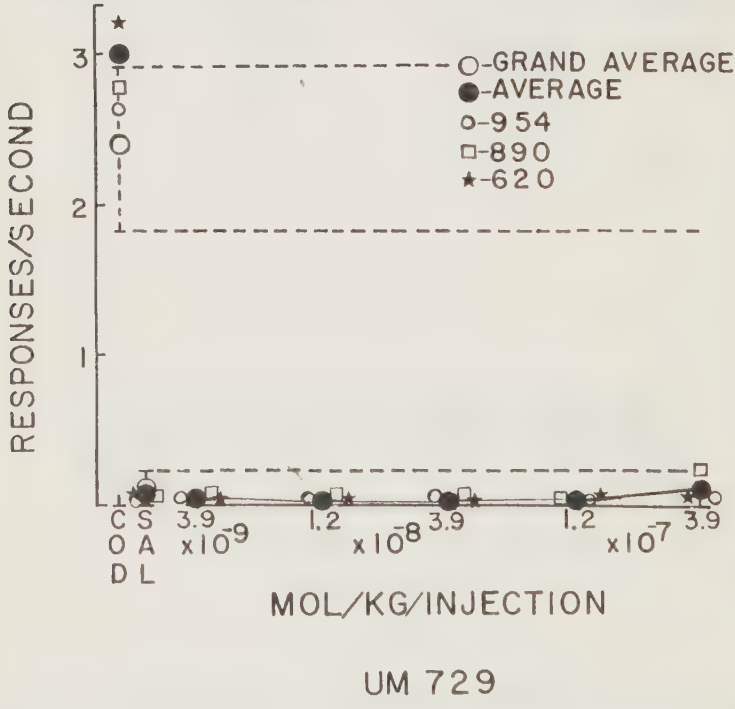
Nilsen: ___

3-Allyl-7-methoxy-1,2,4,5-tetrahydro-3-(3H)-benzazepine hydrochloride

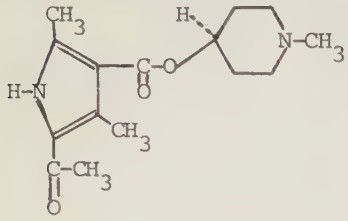
PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

The sedative effects of the drug were reproduced in non-dependent monkeys. Nalorphine (2.0 mg/kg) enhanced these depressant effects, and very high doses of naloxone (8.0 mg/kg) produced only slight antagonism - probably through non-specific mechanisms. Dose tested: SDS, 5.0 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS

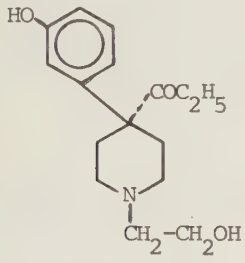


At the doses evaluated, UM 729 was not self-injected at rates above those of saline.

Compounds	Doses Tested (mg/kg)	Effects
UM 1181 NIH 9559  1-Methyl-4-piperidinol 2,4-dimethyl-5-acetylpyrrole-3-carboxylate hydrochloride	SDS 3.0 6.0 NW 3.0	At 3 mg/kg the drug neither suppressed nor precipitated the signs of morphine abstinence. At 6 mg/kg it caused convulsions, and therefore it was not studied at higher doses. MOUSE ANALGESIA, ED_{50} (mg/kg) Hot Plate: 5.0 (4.4-5.8) Nilsen: 13.2 (10.6-16.4) Vehicle: water

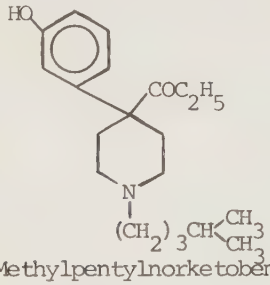
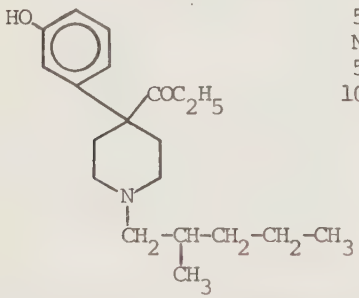
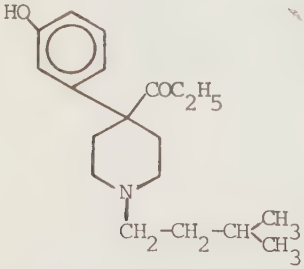
DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

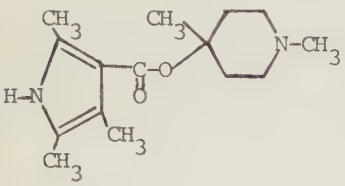
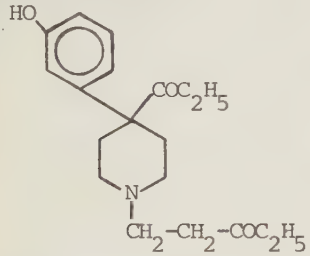
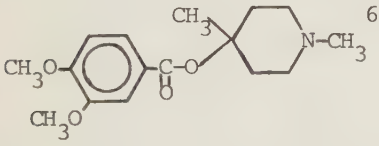
	-Na	+Na	+Na/-Na
EC_{50} (nM)	129,000	397,000	3.07

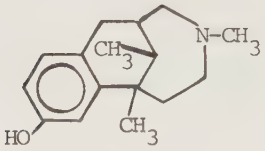
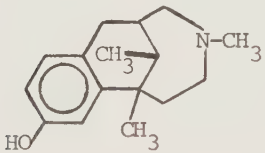
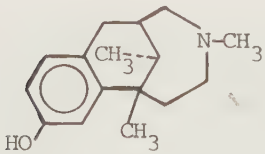
Compounds	Doses Tested (mg/kg)	Effects
UM 1180 NIH 9584  N-2-Hydroxyethylnorketobemidone hydrobromide	SDS 5.0 10.0 NW 10.0	At 10 mg/kg the drug neither suppressed nor precipitated the signs of morphine abstinence. The supply of drug is depleted so higher doses could not be tested. MOUSE ANALGESIA, ED_{50} (mg/kg) Hot Plate: No dose-response. Only one out of ten was affected at 100 mg/kg. Vehicle: water

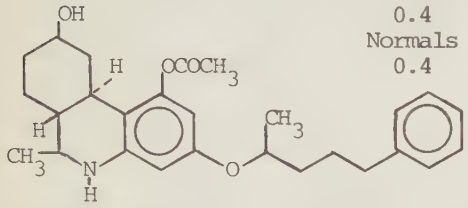
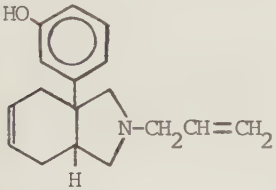
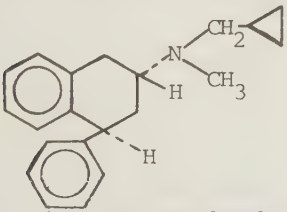
DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

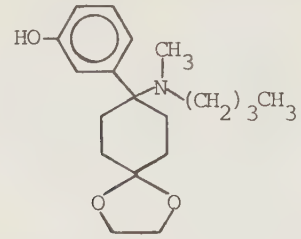
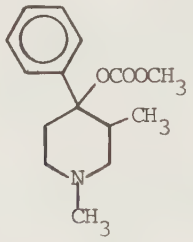
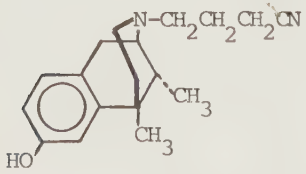
	-Na	+Na	+Na/-Na
EC_{50} (nM)	3304	6550	1.98

Compounds	Doses Tested (mg/kg)	Effects
UM 1198 NIH 9650  N-4-Methylpentylnorketobemidone hydrobromide	SDS 5.0 NW 2.5 5.0	A narcotic antagonist, less potent than nalorphine. The supply of the drug is depleted. Mouse ED_{50}: 3.2 (2.3-4.4)
Vehicle: water		
UM 1197 NIH 9649  N-2-Methylpentylnor ketobemidone hydrobromide	SDS 5.0 NW 5.0 10.0	A narcotic antagonist, less potent than nalorphine. Drug supply depleted. Mouse ED_{50}: Poor dose-response. Eight out of ten affected at 80 mg/kg; two out of ten at 50 mg/kg.
Vehicle: water		
UM 1191 NIH 9636  N-3-Methylbutylnorketobemidone hydrobromide	SDS 4.0 NW 4.0 8.0	It appears to be a weak narcotic antagonist. Higher doses could not be tested because the supply of drug is exhausted. Mouse ED_{50}: 8.3 (6.3-11.0)
Vehicle: water; drug precipitates in bottle as solution cools		

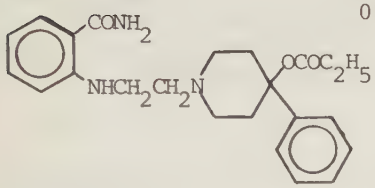
Compounds	Doses Tested (mg/kg)	Effects
UM 1189 NIH 9463 	SDS 2.5 5.0 NW 5.0 10.0	It neither suppresses nor precipitates the signs of morphine abstinence, but at the dose of 10 mg/kg it caused the monkeys to appear pre-convulsive, and so higher doses were not tested. Mouse ED_{50}: 4.6 (3.3-6.4) Nilsen: 6.0 (4.5-7.9)
1,4-Dimethyl-4-piperidinol-4-(2,4,5-trimethylpyrrole-3-carboxylate) hydrochloride Vehicle: water		
UM 1188 NIH 9626 	SDS 4.0 8.0 NW 8.0	At 8 mg/kg, the drug caused very slight abstinence signs in non-withdrawn monkeys. Since the supply was depleted, higher doses could not be tested. Mouse ED_{50}: 7.3 (5.2-10.2) Nilsen: (oral) 14.1 (10.2-19.5)
N-(3-Ketopentyl)norketobemidone hydrobromide Vehicle: water		
UM 1182 NIH 9451 	SDS 1.6 3.2 6.4	At 6.4 mg/kg, the drug seemed to slow the progression of abstinence signs without actually reversing the process. At that dose, the drug seemed to be preconvulsive, and so higher doses were not tested. Drug depleted. Mouse ED_{50}: 3.2 (2.1-4.8) Nilsen: 6.0 (4.5-7.9)
1,4-Dimethyl-4-piperidinol 4-(3,4-dimethoxybenzoate) hydrochloride Vehicle: water		

Compounds	Doses Tested (mg/kg)	Effects
UM 1179 NIH 9565 	SDS 0.3 0.6 1.2 2.4 Normals 2.4	This drug causes such marked motor incoordination and apparent confusion that signs of morphine abstinence cannot be evaluated. There is no evidence that it suppresses abstinence, though one cannot be sure Mouse ED_{50}: 0.57 (0.42-0.78)
(-)-7,12 beta-Dimethyl-9-hydroxy-4-methyl-C-homobenzomorphan Vehicle: 2/3 ethanol; 1/3 Emulphor EL 620		
UM 1178 NIH 9564 	SDS 5.0 10.0	It causes CNS depression without suppressing the signs of morphine abstinence. Drug supply depleted. Mouse ED_{50}: 17.9 (12.3-26.0)
(+)-7,12 beta-Dimethyl-9-hydroxy-4-methyl-C-homobenzomorphan Vehicle: 2/3 ethanol; 1/3 Emulphor EL 620		
UM 1174 NIH 9560 	SDS 1.0 2.0 4.0 Normals 4.0	This drug causes CNS depression with stupor, confusion and motor incoordination but no clear effect upon the progression of morphine abstinence signs. Nalorphine and naloxone had little effect upon its actions. Mouse ED_{50}: 1.5 (1.1-2.0)
dl-9-Hydroxy-7,12 alpha-dimethyl-4-methyl-C-homobenzomorphan Vehicle: water		

Compounds	Doses Tested (mg/kg)	Effects
UM 1159 NIH 9513 	SDS 0.2 0.4 NW 0.4 Normals 0.4	It neither precipitates nor suppresses morphine abstinence signs, but produces a highly atypical form of CNS depression, including dysphoria, confusion and catatonia. These effects were not reversed by nalorphine or naloxone. Mouse ED_{50}: 0.32 (0.24-0.44)
dl-trans-5,6,6a beta,7,8,9,10,10a alpha-octahydro-1-acetoxy-9 beta-hydroxy-6 beta-methyl-3-(5-phenyl-2-pentyloxy)-phenanthridine hydrochloride		
Vehicle: 2/3 ethanol; 1/3 Emulphor EL 620		
UM 1155 NIH 9506 MCV 4140 	SDS 1.0 NW 0.06 0.12 0.25 0.5 1.0	A potent, long-lasting opioid antagonist Mouse ED_{50}: Inactive. Dose-related jumpiness. Nilsen: Inactive. Toxic at 100 mg/kg
2-Allyl-3a-m-hydroxyphenol-2,3,3a,4,7,7a-hexahydro-cis-isoindole		
Vehicle: 1/3 propylene glycol: 2/3 dilute hydrochloric acid		
UM 1153 NIH 9390 	SDS 5.0 NW 5.0	The dose of 5.0 mg/kg of this drug neither suppressed nor precipitated the signs of morphine abstinence. Because of the small quantity of drug available, other doses were not tested. Mouse ED_{50}: 9.1 (5.2-15.9)
trans-3-(N-Cyclopropylmethyl-N-methylamino-1-phenyl-1,2,3,4-tetrahydronaphthalene hydrochloride		
Vehicle: water		

Compounds	Doses Tested (mg/kg)	Effects
UM 1152 NIH 9468 MCV 4131 	SDS 3.0 6.0 NW 3.0	It neither suppresses nor precipitates abstinence signs at 3 mg/kg. At 6.0 mg/kg, it produced convulsions in one of two monkeys Mouse ED_{50}: 5.5 (3.8-7.8)
4-(Methyl-n-butylamino)-4-(m-hydroxyphenyl)-cyclohexanone ethylene ketal hydrochloride Vehicle: water		
UM 1139 NIH 9380 MCV 4112 	SDS 3.0 6.0 12.0	This relatively insoluble compound was administered in 100 per cent propylene glycol. In the doses tested it neither precipitated nor suppressed abstinence signs, though it caused mild CNS depression with decreased skeletal muscle tone. Drug supply depleted. Mouse ED_{50}: 6.0 (4.4-8.3)
1,3-Dimethyl-4-phenyl-4-piperidylmethyl carbonate Vehicle: 100 per cent propylene glycol		
UM 1133A NIH 9369A 	SDS 1.0 2.0 NW 1.0 2.0	The drug precipitates abstinence signs in the non-withdrawn, morphine-dependent monkeys, but it does not intensify the withdrawal signs in monkeys which are already spontaneously withdrawing. It causes signs of CNS depression, including ataxia and stupor. Mouse ED_{50}: 0.9 (0.7-1.2) Nilsen: 0.6 (0.4-0.8)
dl-2-(3-Cyanopropyl)-5,9 alpha-dimethyl-2'-hydroxy-6,7-benzomorphan hydrobromide		

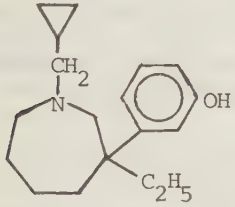
Compounds	Doses Tested (mg/kg)	Effects
UM 891 NIH 8687	SDS 0.003 0.006 0.012 0.025 0.05	The drug suppresses abstinence signs and causes marked CNS depression Mouse ED_{50}: 0.05 (0.04-0.06)



2-(2-(4-Phenyl-4-propionoxypiperidino)ethylamino) benzamide

Vehicle: water

UM 889 NIH 8684	SDS 0.1 NW 0.1 0.2 0.4 0.8 1.6	This drug is a nalorphine-like antagonist, 1/3 as potent. The abstinence syndrome precipitated by this drug differed from that precipitated by nalorphine in that retching and vomiting were minimal with UM 889 Mouse ED_{50}: 0.16 (0.13-0.21)

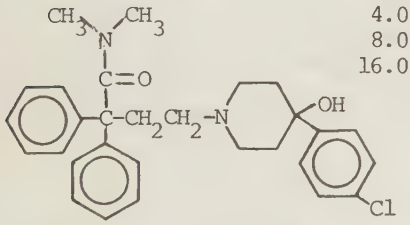


(-)-m-(1-Cyclopropylmethyl-3-ethyl-hexahydro-1H-azepin-3-yl) phenol fumarate

Vehicle: water

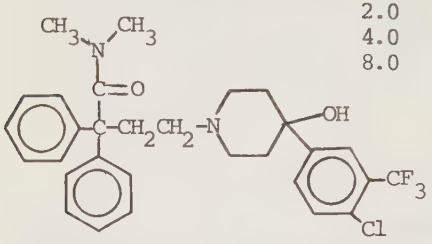
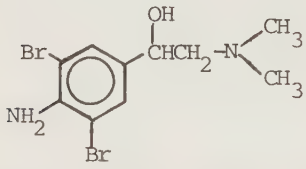
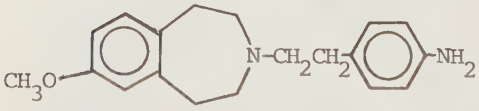
UM 884, UM 899, UM 1095 NIH 8635, NIH 8714, NIH 9230 MCV 4073
Loperamide

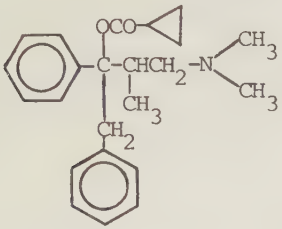
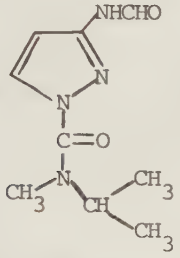
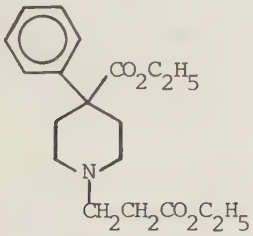
SDS 2.0 4.0 8.0 16.0	At 2.0 mg/kg the drug caused partial, long-lasting suppression of abstinence, whether the drug was dissolved in water, 33% propylene glycol or 100% DMSO. At 4.0 and 8.0 in 33% PG, it produced complete, long-lasting suppression of abstinence. Mouse ED_{50}: 2.6 (2.1-3.2)

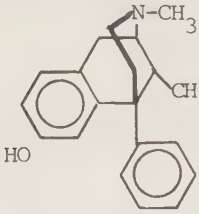
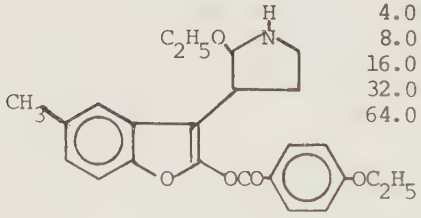
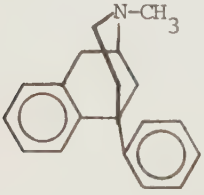


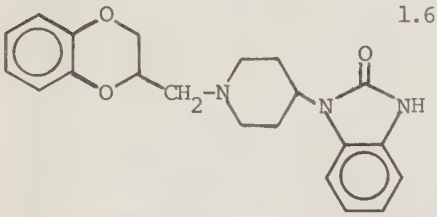
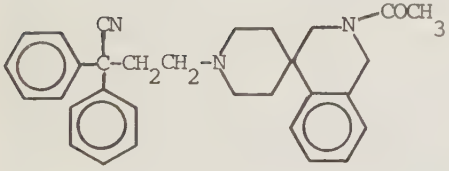
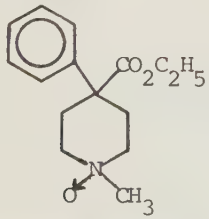
4-(p-Chlorophenyl)-4-hydroxy-N,N-dimethyl-alpha,alpha-diphenyl-1-piperidinebutyramide hydrochloride

Vehicle: water, 33% propylene glycol or 100% dimethylsulfoxide

Compounds	Doses Tested (mg/kg)	Effects
UM 866, UM 900 NIH 8636, NIH 8715		
	SDS 2.0 4.0 8.0	When given in 50% propylene glycol, it caused long-lasting suppression of abstinence signs and CNS depression. When given in DMSO, it had no apparent effect other than causing abscesses.
		Mouse ED_{50}: 2.9 (2.4-3.5)
4-(4-Chloro-alpha, alpha, alpha-trifluoro-m-tolyl)-4-hydroxy-N,N-dimethyl-alpha,alpha-diphenyl-1-piperidinebutyramide HCl		
Vehicle: 50 per cent propylene glycol or 100 per cent DMSO		
UM 762 NIH 8444	SDS 1.0 2.0 4.0 8.0 16.0 NW 16.0	At a dose of 16 mg/kg, it seemed to intensify the signs of abstinence, but this dose in 2 non-withdrawn monkeys did not precipitate abstinence.
		Mouse ED_{50}: 2.2 (1.8-2.7)
4-Amino-3,5-dibromo-alpha-((dimethylamino)methyl)benzyl alcohol hydrochloride		
Vehicle: water		
UM 720 NIH 8366	SDS 4.0 8.0 16.0	It neither suppresses nor precipitates abstinence signs, but at the highest dose caused CNS stimulation. Animals appeared pre-convulsive.
		Mouse ED_{50}: 9.8 (8.0-12.1)
3-(p-Aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3-(3H)-benzazepine dihydrochloride		
Vehicle: water		

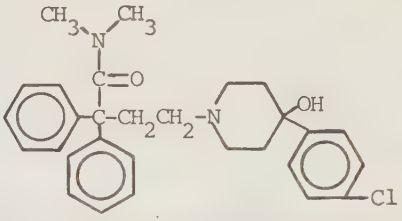
Compounds	Doses Tested (mg/kg)	Effects
UM 706 NIH 8400 	SDS 2.0 4.0 8.0 16.0 32.0	Nearly complete suppression of abstinence signs at 32.0 mg/kg, a dose which caused severe tremors and marked apprehension Mouse ED_{50}: 11.5 (9.3-14.3)
2-Cyclopropylcarbonyloxy-4-dimethylamino-3-methyl-1,2-diphenylbutane Vehicle: water		
UM 635 NIH 8251 	SDS 1.0 32.0 NW 0.5 1.0 2.0 4.0 8.0 16.0 32.0	This drug is a weak nalorphine-like antagonist. Its dose-response curve is flat and has a low maximum. The drug also has sedative properties. Mouse ED_{50}: 1.9 (1.7-2.1)
N-Isopropyl-N-methyl-3-formamido-1-pyrazole carboxamide Vehicle: water		
UM 625 NIH 8242 	SDS 2.0 4.0 8.0 16.0	It suppresses the signs of morphine abstinence. At the highest dose it caused coma and a slight convulsion. Mouse ED_{50}: Inactive. Only two of ten affected at 100 mg/kg
1-(beta-Carbethoxyethyl)-4-carbethoxy-4-phenylpiperidine hydrochloride Vehicle: water		

Compounds	Doses Tested (mg/kg)	Effects
UM 623, UM 668 NIH 8240, NIH 8299 	SDS 0.5 1.0 2.0 4.0 8.0 NW 2.0 4.0 8.0	GPA 1657 A nalorphine-like antagonist, approximately 20 times less potent. A Primary Addiction Study of this compound was included in the ANNUAL REPORT of 1967. Mouse ED_{50}: 0.18 (0.15-0.20)
(-)-2'-Hydroxy-2,9 beta-dimethyl-5-phenyl-6,7-benzomorphan hydrochloride		
Vehicle: propylene glycol plus water		
UM 610 NIH 8225 	SDS 1.0 2.0 4.0 8.0 16.0 32.0 64.0	This drug does not suppress the signs of morphine abstinence, but in a Primary Addiction Study (see ANNUAL REPORT of 1963) it was found to produce mild abstinence signs of its own - mostly hyperirritability and tenderness, with few if any GI signs. Mouse ED_{50}: 2.3 (2.0-2.6) Oral: 47.7 (42.9-53.0)
2-(4-Ethoxybenzoyl)-5-methyl-3-(2-pyrrolidinoethoxy)-benzofuran hydrochloride		
Vehicle: water		
UM 604 NIH 8216 	SDS 1.0 2.0 4.0 8.0 16.0 NW 16.0 32.0	This drug is a weak nalorphine-like antagonist, with CNS stimulant properties and a low margin of safety Mouse ED_{50}: 6.1 (5.3-7.1) Nilsen: 5.4 (3.7-7.9)
2-Methyl-5-phenyl-6,7-benzomorphan hydrobromide		
Vehicle: water		

Compounds	Doses Tested (mg/kg)	Effects
UM 461 NIH 8034 	SDS 0.4 0.8 1.6	A dose of 1.6 mg/kg of this drug is required to produce complete suppression of all morphine abstinence signs. It produces more sedation than would an equivalent dose of morphine. Mouse ED_{50}: 2.0 (1.7-2.3) Oral: 19.1 (15.8-23.0)
1-(2-(1,4-Benzodioxanyl)-methyl)-4-(2-oxo-1-benzimidazolinyl-piperidine Vehicle: water		
UM 485 NIH 8062 	SDS 0.003 0.01 0.015 0.03 0.06 0.125 0.25 2.0	In a dose of 0.03 mg/kg it produces complete suppression of morphine abstinence plus intermediate level CNS depression Mouse ED_{50}: 0.032 (0.028-0.037) Oral: 0.46 (0.40-0.53)
2-Acetyl-1,2,3,4-tetrahydroisoquinoline-4-spiro-4'-(1'-(3-cyano-3,3-diphenylpropyl)) piperidine hydrochloride Vehicle: propylene glycol		
UM 149 NIH 7413 	SDS 5.0 10.0 20.0	The tested doses failed to to suppress the signs of morphine abstinence. Mouse ED_{50}: Inactive. Only one out of ten affected at 250 mg/kg
4-Carbethoxy-1-methyl-4-phenylpiperidine N-oxide hydrobromide Vehicle: water		

314-300 O -80 - 27

UM 884 (NIH 8635); UM 899 (NIH 8714); UM 1095 (NIH 9230); Loperamide



4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-alpha,alpha-diphenyl-1-piperidine butyramide hydrochloride

Previous studies in this laboratory. Under three different code numbers, this compound has been submitted for single-dose-suppression studies:

As UM 899 (NIH 8714), the material was dissolved in 100 per cent dimethylsulfoxide. In this solvent, a dose of 4.0 mg/kg caused no apparent effect, while a dose of 16 mg/kg produced a very slight amelioration of opioid abstinence signs, but caused abscesses at the injection sites. Therefore, the study of UM 899 was discontinued.

As UM 884 (NIH 8635), this drug was dissolved in 30 per cent propylene glycol. At 2.0 mg/kg, it produced partial suppression of morphine abstinence signs; at 4.0 mg/kg, the suppression was almost complete; at 8.0, the drug caused complete suppression of abstinence and also produced sedation. The effects were slow in onset (peaking in 3 to 4 hours) and the abstinence suppression was of long duration (12 hours at 8.0 mg/kg).

Oral administration of 8.0 mg/kg of this drug produced complete suppression of abstinence signs, and this effect was still apparent 12-14 hours after drug administration.

Normally, single dose suppression tests are performed blindly, with the compounds identified only by code number. When this drug was re-investigated as UM 1095 (NIH 9230), its identity and structure were known to the investigators. At a dose of 2.0 mg/kg, it was given to different animals in water solution, in 30 per cent propylene glycol and in 100 per cent DMSO. The results with these three solvents were similar, with the drug showing marked, long-lasting, abstinence-relieving properties.

Dosage schedule. During this Primary Addiction Study, the dose of loperamide was changed several times, in an attempt to maintain drug effects between injections but still not produce dangerous levels of CNS depression. The doses which were used were:

Day 1	- 2.0 mg/kg, every 6 hours
Days 2-6	- 0.5 mg/kg, every 6 hours
Days 7-9	- 1.0 mg/kg, every 6 hours
Days 10-15	- 2.0 mg/kg, every 6 hours

Days 16-20	- 1.0 mg/kg, every 6 hours
Days 21-29	- 2.0 mg/kg, every 8 hours
Days 30-34	- 2.0 mg/kg, every 6 hours
Day 35	- abrupt withdrawal

Animals. This study was started with monkeys numbered 820, 821 and 822. Within 24 hours, monkey #822 had died of acute, drug-induced respiratory depression. That animal was replaced by monkey #824 for the remainder of the study.

Acute effects. Loperamide caused morphine-like CNS depression, with the monkeys staring into space and showing body sag, muscle weakness, occasional scratching and slight pupil dilatation. At the initial dose of 2.0 mg/kg every 6 hours, there was an apparent cumulation of the drug, because all three animals developed respiratory depression. One animal died, as noted above, and the other two were given naloxone, 2.0 mg/kg, which reversed the effects of loperamide.

The doses of 0.5 and 1.0 mg/kg produced milder CNS depression, and it appeared that tolerance developed to these doses upon repeated administration, such that after several days of drug administration, the drug effects did not last through the six-hour interinjection interval. On the other hand, at a time when tolerance had developed to the lower doses, the administration of 2.0 mg/kg every six hours produced progressively more severe muscle weakness and ataxia--suggesting again that cumulation was occurring at this dose. On the other hand, the every-eight-hour administration of 2.0 mg/kg did not sustain a drug effect throughout the interinjection interval. Thus, no truly satisfactory injection schedule was achieved in this study.

Physical dependence. A naloxone challenge was performed on the 14th day of the study, at a time when the monkeys had been receiving loperamide at the highest dose (2.0 mg/kg every 6 hours) for several days. The precipitated abstinence syndrome was very severe -- in the range between 6 and 7 on the Seevers scale. Signs appeared within two minutes of naloxone administration. All three monkeys screamed constantly, showed severe autonomic signs and were so sick that they could not move. Though the abstinence signs decreased in intensity with the passage of time, they were still apparent to a certain extent for six hours, until the monkeys received a dose of loperamide.

On the 16th day, nalorphine was used to precipitate abstinence signs, which were less severe and somewhat different in character from those seen two days earlier with naloxone. After nalorphine, the monkeys showed marked irritability when handled, and this irritability was of a general nature, rather than localized to the abdominal area. The animals were irritable towards each other, though there were periods during which they became calm, sitting quietly, ignoring one another and staring into space. The severity of the nalorphine-precipitated abstinence was graded as slightly greater than 4 on the Seevers scale.

Abrupt withdrawal of loperamide occurred on the 35th day of the study. A typical opioid withdrawal syndrome developed slowly in each of the three animals. For the first 24 hours, there were essentially no signs. Between 60 and 90 hours after the last dose of loperamide, the abstinence syndrome reached a level of approximately 4 on the Seevers scale; by 120 hours, the signs had become minimal; after 160 hours, the signs were completely gone.

Summary. Loperamide is a relatively insoluble drug with long-lasting opioid properties. Acute administration produces morphine-like CNS depression which is antagonized by naloxone. It relieves the abstinence syndrome in morphine-dependent monkeys. On chronic administration, there appears to be both cumulation and tolerance development. Physical dependence develops, such that opioid abstinence signs appear gradually when loperamide administration is discontinued abruptly or develop acutely when the animals are challenged with nalorphine or naloxone.

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Papers Read by Title But Not Presented at the 41st Annual CPDD Meeting

Effects of Alcohol Abuse on Progression of Liver Disease in Methadone-Maintained Patients

Beverley, C. L.; Kreek, M. J.; Wells, A. O.; Curtis, J. L.

To determine whether chronic abuse of alcohol produced rapid deterioration of liver function in methadone-maintained patients, a 2-year prospective study was conducted in a single methadone maintenance treatment clinic in New York City (1-8). Sixty-eight, or 31 percent of patients enrolled in treatment were identified as chronic alcohol abusers at the beginning of the prospective study period.

At the end of the 2-year period, 28 (41 percent) of patients initially identified as alcohol abusers remained in methadone maintenance treatment; 55 percent of the remaining non-alcohol-abusing clinic population remained in treatment at the end of the 2-year period.

At least 54 percent of alcohol-abusing patients remaining in methadone maintenance treatment during the study period showed improvement or no change in liver function tests (SGOT, bilirubin, alkaline phosphatase). Analysis of similar data available on these 28 patients for up to 4 years preceding the study showed that liver function had either improved or not changed in 61 percent over a 2 to 6-year period. Data were available for 3 years or longer for 72 percent of these patients.

At the end of the prospective period, 40 patients (59 percent) initially identified as alcohol abusers had terminated treatment. Comparable liver function test data are available for only 2 of these patients during the prospective study period. However, during the combined 2-to 6-year period, data were available for 19 patients (48 percent). Improvement or no change in liver function was observed in only 20% of these patients. There were no deaths due to liver disease in the alcohol-abusing patients.

Liver function tests of 28 randomly selected non-alcohol-abusing methadone-maintained patients enrolled in the clinic throughout the prospective study period were evaluated retrospectively. Comparable test data were available for 17 patients (61 percent)

during the study period. Improvement or no change in liver test values was observed in 54 percent of these patients during 2 years, and 75 percent in the combined 2 to 6-year period.

These data show that there was no rapid deterioration in liver function, as evidenced by laboratory tests, in alcohol-abusing methadone-maintained patients remaining in treatment. Since 41 percent of the alcohol-abusing patients remained in methadone treatment for at least 2 years and, of these, 72 percent had been followed for longer than 3 years, the commonly held opinion that methadone maintenance treatment for the alcoholic heroin addict or former addict is ineffective and possibly hopeless may no longer be valid (9,10).

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Modification of Treatment Compliance as a Function of Contingent Payment Manipulations

Grabowski, J.; O'Brien, C. P.; Greenstein, R.; Long, M.; Steinberg-Donato, S.; Ternes, J.

A problem common to treatment regimens is that of establishing compliance (Swinyard, 1975). However, as Zifferblatt (1975) has noted, noncompliance should be amenable to change using behavior modification techniques. Stitzer and Bigelow (in press) and others (Stitzer, Bigelow, and Liebson, in press; Liebson, Tomassello and Bigelow, 1978) have suggested specific behaviorally based procedures which may enhance compliance in drug treatment programs.

The degree of compliance which can be inherently generated by a specific treatment form is illustrated by pharmacological agents used as adjuncts in treatment of opiate use. Methadone is itself a positive reinforcer and this in combination with existence of physical dependence contributes to continuing attendance at a clinic where other treatment can be provided. LAAM is only mildly reinforcing but produces physical dependence and thus continued access to other treatment options is probable. Naltrexone, an opiate antagonist, does not generate physical dependence, has no immediate positive reinforcing properties and thus, like many other treatment forms, has no inherent characteristics increasing the probability of regular "treatment-seeking behavior."

A patient expressing a "strong" desire to remain opiate free and taking naltrexone is not provided with a built in mechanism in the pharmacological treatment to engage in persistent "treatment-seeking behavior." Therefore treatment visits may be irregular or terminate early in the opiate free period. Abbreviated duration may be disadvantageous since it has been reported that successful outcome is correlated with duration of naltrexone treatment (Resnik and Schuyten-Resnik, 1976) and irregularity of naltrexone ingestion precludes effective opiate blockade and thus the possibility of reinitiation of opiate use emerges.

Meyer et al. (1976) noted that the behaviorally based procedure of making small daily payments increased likelihood of clinic attendance by patients taking naltrexone. Curran, Doyle and

Savage (1977) implemented an equivalent reinforcement schedule procedure with less clear benefit. Since combinations of response and temporal requirements constituting reinforcement schedules have been demonstrated to be powerful determinants of rate and pattern of behavior it might be expected that effective alternatives to the simple 1:1 payment procedure may further enhance compliance. The purpose of the present study was to examine the effects of payment and scheduling on compliance with a naltrexone treatment regimen.

METHOD

Subjects: Nine individuals (age range 24-30) with a past history of opiate use who were being treated with naltrexone served as subjects. Naltrexone was one treatment choice available to patients and thus involve self-selection.

Setting: The treatment setting was the University of Pennsylvania/ Philadelphia Veterans Administration Hopsital Drug Dependence Treatment Center. Diverse services are provided by a variety of professional staff members.

Procedure: Individuals who decided in favor of treatment with naltrexone were given the opportunity for involvement in the study. Each patient was asked to read an "Information and Consent" form which included multiple choice questions requiring correct responses (Grabowski, O'Brien, and Mintz, 1979). The patients' questions were then answered and they were asked to sign the form if they were interested in participating.

Opiate detoxification and initiation of preliminary low doses of naltrexone were accomplished on an inpatient basis followed by initiation of a thrice weekly regimen on an outpatient basis. Patients entering the payment study were assigned to schedule groups sequentially, including: Continuous Reinforcement (CRF; for which payment occurred on each visit), a Fixed Interval (FI; payment once each week), Fixed Ratio (FR; payment every third visit) or a Variable Ratio (VR; payment mean every third visit) schedule. Patients received $3.35 each day for the first three visits. In subsequent weeks the several reinforcement schedules were initiated. The CRF and VR reinforcement schedules were deleted as maintenance schedules later in the study. After eight weeks on the initial schedule, conditions were reversed. Subjects on response-based schedules (CRF, FR, VR) were switched to the time-based (FI) schedule and those receiving payment under time-based (FI) contingencies were switched to the response-based (FR) procedure. After four weeks the conditions were again reversed and thus the original schedules were reinstated.

The total possible payment per month ($40.20) was the same under all schedules: CRF payments were $3.35 each, while FR, VR and FI payments were $10.05. Payments were dispensed by a person not involved in treating naltrexone patients.

In general, providing payment appears to increase the duration of treatment with naltrexone. Prior to introduction of the payment schedules retention through the first month of treatment was 60% (74 of 125) of all patients completing the naltrexone induction sequence. For payment schedule patients, 89% (8 of 9) remained in treatment for at least one month. The percentage of patients departing from treatment during the first four months continued to increase more rapidly for those not receiving payment (Figure 1).

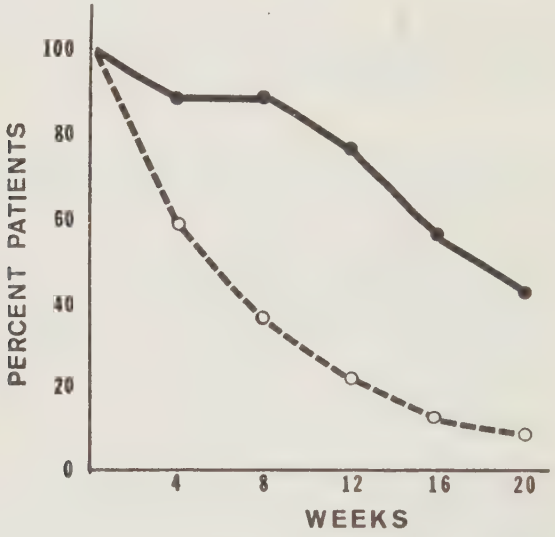

Figure 1: Percentage of naltrexone regimen patients remaining in treatment over successive four-week periods. Patients (N=9) in the study received payment contingent on attendance/ingestion (●——●). Previously patients (N-126) had received payment for other procedures and it was not contingent on adherence to the naltrexone regimen (O----O). © 1979, Marcel Dekker, Inc.[1]

The pattern of attendance suggests differences were due in part to the prevailing maintenance payment schedule. Patients attended the clinic and ingested naltrexone on 88.0% (140 of 159) of the scheduled visits when payment was response-based; that is when payment was directly contingent on number of doses ingested as in the CRF, FR, and VR schedules. However, when payment was time-based, (FI), and "missed doses" did not necessarily delay payment, patients attended the clinic and ingested naltrexone on 72.8% (107/147) of the scheduled visits. The differences between cumulative attendance/naltrexone ingestion data for response and time-based schedules are statistically significant ($p < .001$).

When patients attended under the time-based schedule, payments were made on Friday or on the first visit thereafter. All Friday (payment day) appointments for naltrexone ingestion were kept when the prevailing schedule was time-based. Therefore, the cumulative percentage of "missed doses" (27.2%) under the time-based schedule occurred on Monday or Wednesday, i.e., the days on which no payment was scheduled. When payment was contingent on the number of naltrexone doses ingested, no pattern of "missed doses" was evident. That changes in the pattern of attendance generally covaried with systematic schedule reversals indicates that control was generated by the maintenance schedule (b,c,d, Figure 2). However, some patients ingested naltrexone consistently,

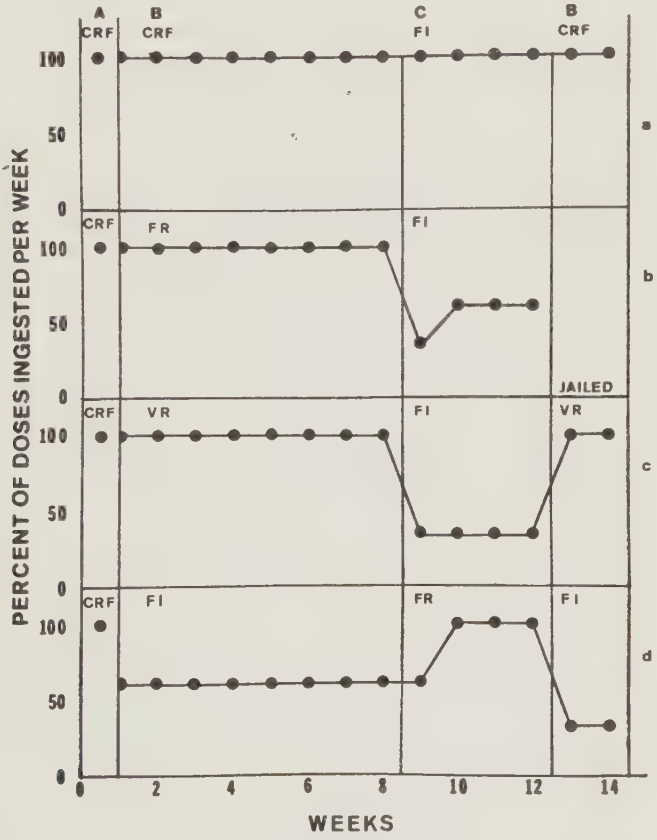

Figure 2: Data for 4 patients illustrating patterns of attendance as a function of the maintenance reinforcement schedule. In b, c and d, clinic attendance/naltrexone ingestion covaried with schedule changes. Data in a is for patient whose consistent attendance continued during the FI schedule which "permitted" missed visits. (a) CRF, continuous reinforcement; (b) FR, fixed ratio; (c) VR, variable ratio; (d) FI, fixed interval. © 1979, Marcel Dekker, Inc.[1]

regardless of the reinforcement schedule (a, Figure 2) which indicates, as might be expected, that payment was only one of several determinants of the behavior.

DISCUSSION

This preliminary study permitted evaluation of several factors modulating compliance to a naltrexone treatment regimen. The results support those of Meyer et al. (1976) which indicated that monetary reinforcement may increase naltrexone treatment duration. In addition the results suggest that use of specific schedules of reinforcement may reduce inconsistent attendance/naltrexone ingestion patterns, thereby reducing the problem of inadequate opiate blockade.

Response-based schedules (CRF, FR, VR) generated a more regular attendance pattern than time-based (FI) schedules, which was desirable. The VR schedule produced the most consistent behavior, but the irregularity of payments was a source of continual complaints. As a result, VR payments were not viewed as acceptable, based on therapeutic considerations. Although the CRF schedule was both effective and considered acceptable by patients, it was cumbersome to administer in the prevailing system and was subsequently omitted. Clearly this problem might not arise in other clinics, and it is not necessarily a reason to exclude the schedule. However, use of the CRF schedule was continued during the first week of treatment in order to establish the procedure's "credibility" with the patients.

In general, observations indicate that the FR schedule was optimal for several reasons: it provided predictable reinforcement for naltrexone ingestion; the explicit consequence for missed doses was delay of payment; and finally patients perceived the schedule as fair and the most desirable of those available, since it provided consistent meaningful payment each week.

A question of some concern was whether the monetary payments available to patients were adequate reinforcers. The total amount of $40.20 each month appeared sufficient to significantly increase the duration of treatment. Larger weekly payments or additional monthly "bonuses" for regular attendance would probably be even more effective. Subsequent experience with several patients having substantial incomes produced mixed results with one insisting on payment and others ignoring it.

Finally, it has been suggested that when a patient misses a naltrexone dose, he is making an explicit behavioral statement of intent to use opiates. It has also been suggested that the patient is "testing his will power." Although fairly simplistic, both patterns of behavioral statement should be considered. An alternative view is that a primary determinant of missed doses is absence of both positive reinforcing consequences and the negative reinforcers associated with physical dependence. From this perspective it is essential to differentiate short-term

behavioral variability and long-term goals. The patient with a history of opiate use enters naltrexone treatment with a long-term goal established and has overcome several obstacles to do so. It seems unreasonable to suggest that by missing a dose of naltrexone he is abrogating long-term goals.

Naltrexone treatment is a possible means for individuals to achieve the goal of opiate independence. However because naltrexone ingestion is not intrinsically reinforcing, patients may miss doses. Such omissions will weaken the antagonist-generated blockade, and in combination with availability of opiates this may result in relapse for the former user. Since therapeutic techniques do exist to increase compliance it seems reasonable to make use of them. That providing extrinsic reinforcers does not have the elegance of the elusive concepts of "will power" or "good motivation" should not serve as a deterrent to their use.

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FOOTNOTE

1. Figure 1 and figure 2 and a modified version of this text originally appeared in Grabowski, J.; O'Brien, C.P.; Greenstein, R.; Long, M.; Steinberg-Donato, S.; and Ternes, J.; Effects of contingent payment on compliance with a naltrexone regimen; The American Journal of Drug and Alcohol Abuse; Vol. 6, No. 3; copyright 1979; Marcel Dekker, Inc; New York, New York. They are used with permission of Marcel Dekker, Inc., and may not be further reproduced without their specific permission.

The Effect of l-Alpha Acetyl Methadol in Morphine-Dependent Rats

Riley, A. L.; Etherton, D. S.; Shapiro, R. M.

L-alpha acetyl methadol (LAAM) has recently been introduced as one alternative to methadone in the maintenance therapy for narcotic addiction (Blaine 1978; Blaine and Renault, 1976). Before it can be considered a viable alternative, however, several issues must be assessed. First, it must be determined if LAAM can adequately substitute for morphine in narcotic-dependent subjects, and as such, prevent the occurrence of withdrawal. Secondly, it must be determined if subjects maintained on LAAM following morphine withdrawal become dependent on this substitute.

Several reports using rats as subjects have demonstrated that LAAM given continuously via intraperitoneal or intravenous infusion can partially substitute for morphine in morphine-dependent subjects (Patrick, Dewey, and Harris, 1976; Young, Steinfels, and Khazan, 1978). Under both administration techniques, dependence to LAAM was reported. Clinical research has basically extended these findings to humans, i.e., substitution with dependence (see Blaine, 1978).

The present experiments examined the substitution potential and dependence liability when LAAM is administered intermittently via daily intraperitoneal injection.

EXPERIMENT 1

Procedure

The subjects were 24 experimentally naive, female rats of Long-Evans descent, approximately 90 days of age. Each subject was maintained in an individual wire mesh cage and given ad libitum access to food and water throughout the experiment. All subjects were maintained on a 12-hr light/12-hr dark cycle for the duration of the study. Ambient temperature was maintained at 72° ± 2° F. Body weights were monitored daily, 15 min prior to drug or control injection.

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Phase I: Morphine maintenance. Following a week of daily injections of distilled water, subjects were randomly assigned to four groups (n=6 for each group). Groups MS and ML were given daily intraperitoneal (IP) injections of morphine sulfate (80 mg/kg) for 21 consecutive days. Groups SS and SL were given volumetrically equivalent, daily IP injections of distilled water for 21 consecutive days.

Phase II: LAAM substitution. On the day following the last morphine or control injection (Day 29), Groups ML and SL were injected IP with LAAM (8 mg/kg) and Groups MS and SS were injected with distilled water. These injections were given daily for 14 consecutive days.

Phase III: LAAM withdrawal. On the day following the last LAAM or control injection (Day 44), all subjects were injected IP with distilled water. These water injections were given for seven consecutive days.

Results

The substitution by and withdrawal from LAAM are indexed by the maintenance and loss, respectively, of body weight from baseline.

While there were no differences in body weights among groups during the initial seven days of water injections (Days 1-7), a significant difference emerged among groups when differential treatments were administered. Groups MS and ML, subjects receiving morphine during Phase I, significantly decreased in body weight in relation to the water-injected groups. With repeated injections of morphine, Groups MS and ML showed partial recovery to baseline, suggesting that tolerance to the effects of morphine had occurred during this maintenance phase.

Figure 1

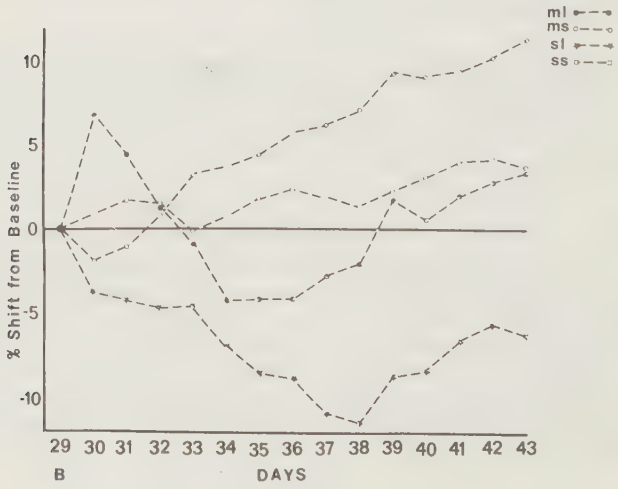


Figure 1 presents the percent shift in body weight from baseline (B) for each group during Phase II, LAAM substitution. On the first day of Phase II (Day 29) when water was given in place of morphine to morphine-dependent rats (Group MS), there was a decrease in body weight (2-3 percent) 24 hr following the water injection, suggesting spontaneous withdrawal from morphine. With repeated water injections, body weights for Group MS gradually recovered, approximating a normal rate of weight increase after five days of morphine withdrawal. On Day 29, when LAAM replaced morphine in morphine-dependent rats (Group ML), morphine withdrawal was not evident, i.e., LAAM prevented the weight loss seen in Group MS. Instead of a body weight decrease, Group ML significantly increased in body weight. That subjects given LAAM without a prior history of morphine (Group SL) decreased in body weight following the LAAM injection suggests that cross-tolerance developed between morphine and LAAM in Group ML. With repeated LAAM injections, Group ML gradually decreased in body weight below the pre-LAAM baseline, recovering to baseline after 11 daily injections. Group SL further decreased in body weight with repeated injections. After 11 daily injections, these subjects gradually increased in weight, although never recovering to their pre-LAAM baseline. Group SS, subjects maintained on water throughout the first 43 days, showed normal body weight increases over repeated water injections.

Figure 2

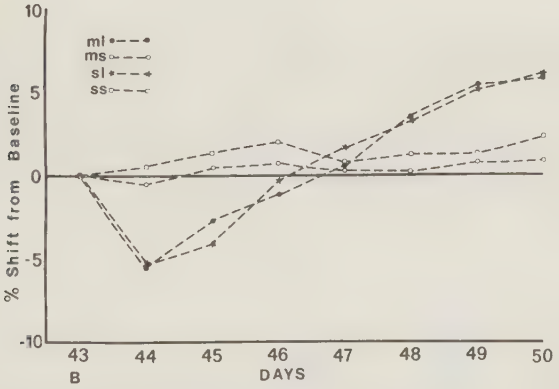


Figure 2 presents the percent shift in body weight from baseline (B) for each group during Phase III, LAAM withdrawal. On the first day of LAAM withdrawal (Phase III), when all subjects were injected with distilled water, significant differences emerged among groups. Both Groups ML and SL, subjects previously maintained on LAAM, showed a significant reduction in body weight (5 percent) 24 hr following the water injection. While at 24 hr withdrawal from LAAM (5 percent baseline shift) is more severe

than withdrawal from morphine (2-3 percent, see figure 1), weight losses following shorter intervals, e.g., 6 hr after either morphine or LAAM withdrawal, are much more severe for morphine (14 percent) than LAAM (3 percent). Group SS and MS showed no significant change in body weight in response to water injection. With repeated injections of water, both Groups ML and SL gradually increased in body weights, recovering to baseline within 4-5 days following LAAM withdrawal. Group SS and MS gradually increased body weights over repeated water injections.

Discussion

While LAAM was effective in preventing withdrawal from morphine, the substitution was incomplete, i.e., there was an increase in body weight followed by a gradual decline below baseline weight with repeated LAAM injections. This initial increase and subsequent decrease could reflect the hyperphagic (Riley, Schoonover, and Shapiro, 1978) and debilitating (see Group SL) effects, respectively, of this relatively high dose of LAAM. The dependence to LAAM may also be a function of the dose of LAAM. At this dose, the substitution potential of LAAM is partially offset both by the incomplete substitution and rapid dependence liability. To determine if these effects are characteristic of LAAM in general, Experiment 2 examined the substitution potential of LAAM across a range of doses.

EXPERIMENT 2

Procedure

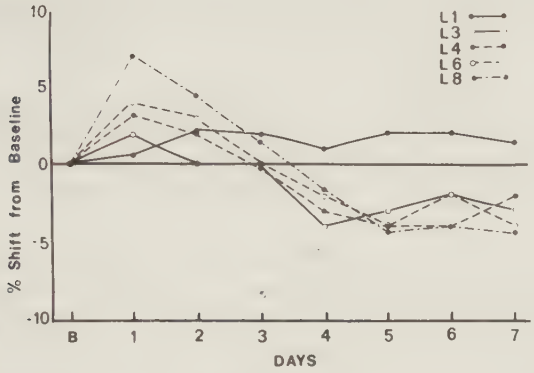
In all unspecified details, Experiment 2 is similar to Experiment 1. Following adaptation to water injections, all subjects were maintained on morphine for 14 consecutive days. At this point different groups of subjects (n=6 for each group) were injected with 1, 3, 4, or 6 mg/kg of LAAM. These injections were given daily for seven consecutive days. Following the seven days of LAAM substitution, all subjects were injected with distilled water to assess spontaneous withdrawal from LAAM.

Results

As in Experiment 1, when LAAM substituted for morphine in morphine-dependent subjects, there was no immediate evidence of withdrawal from morphine. Similar to Experiment 1, at doses of 3, 4, and 6 mg/kg, there was a significant increase in body weight followed by a gradual decrease below baseline weight with repeated injections of LAAM. Figure 3 presents the percent shift in body weight from baseline (B) for each group during this phase of LAAM substitution for morphine. The data for Group ML (8 mg/kg) from Experiment 1 is included in figure 3 for comparison. As figure 3 presents, this initial increase and subsequent decrease was not evident for subjects receiving the lowest dose of LAAM, 1 mg/kg. Subjects in this group maintained

normal growth over this seven day period.

Figure 3



When water replaced LAAM during withdrawal, all groups decreased in body weight, suggesting dependence to LAAM. This decrease, however, was significantly less at the 1 mg/kg dose (2 percent shift from baseline) than at the higher doses (5 percent shift).

Discussion

It is clear from the data that LAAM can substitute for morphine in morphine-dependent rats. Only at 1 mg/kg, however, was this substitution complete, i.e., there was no initial increase and subsequent decrease characteristic of the higher doses. That the substitution is complete at this dose of LAAM suggests that the incomplete substitution seen in the other groups may result from the hyperphagic and debilitating effects of the higher doses of LAAM.

While 1 mg/kg LAAM was effective as a substitute, similar to the higher doses, dependence did occur at this dose. Although withdrawal from this dose was less severe than that at the intermediate and high doses, the dependence liability of LAAM in general may in part offset its substitution potential. It is possible, however, that with even smaller doses of LAAM substitution would be complete without dependence.

The present experiments, and those of Patrick, Dewey, and Harris (1976) and Young, Steinfels, and Khazan (1978), suggest that LAAM may be effective in the drug maintenance therapy of narcotic addiction. Such conclusions, however, should be cautiously made until such demonstrations of substitution efficacy more closely parallel clinical parameters, e.g., the spaced administration of LAAM for both morphine and methadone.

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Outcome for Structural Family Therapy With Drug Addicts

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This paper presents some treatment followup results from a research program evaluating the efficacy of brief family therapy with heroin addicts. Preliminary data with a smaller group of subjects (Stanton & Todd, 1976) indicated that this treatment approach showed promise for reducing addiction. The present study extends the findings to a six-month posttreatment period.

BACKGROUND

Reviews of the literature (Harbin & Maziar, 1975; Seldin, 1972; Stanton, 1978, 1979), indicate that there is a fairly large and growing body of literature on the nature and importance of family factors in heroin addiction. The consensus of these reviewers is that drug addiction is a symptom maintained to serve family functions. Frequently it fits into a repetitive pattern such that when the addict starts to abstain or "clean up" family turmoil ensues and his parents' marital problems become exacerbated; when he gets "dirty" again the family stabilizes and reunites in relation to him and his problem (Alexander & Dibb, 1975; Harbin & Maziar, 1975; Schwartzman, 1975; Stanton, 1978, 1979, Stanton, et al, 1978). This pattern resembles that noted by Haley (1973, 1976) and others for schizophrenics, in which improvement in the identified patient results in increased difficulty between his parents. In another parallel to schizophrenics, the most common family relationship structure reported for male addicts is one in which the mother is dominant and overprotective, while the (often alcoholic) father is detached, uninvolved, or absent. Of particular note is the frequency of contact between adult addicts and their mothers. This was first reported by Vaillant (1966) who found that 72 percent of his addicts still lived with their mothers at age 22. When those whose mothers died prior to the addicts' 16th birthday were deducted, the percentage rose to 90 percent. A 1972 survey of our own taken among 85 addicts at the Philadelphia VA found that of those with living parents, 82 percent saw their mothers and 58 percent saw their fathers at least weekly; 66 percent saw their mothers daily. The figures become even more impressive when one realizes that the average age of these men was 28 and all had been

in the military for at least several months.

While therapy has gone on at a number of centers and is gaining more visibility and momentum, it has generally not been accompanied by evaluative efforts. In their comprehensive review of the outcome research on marital and family therapy Gurman and Kniskern (1978) located over 200 studies and only two (including our own; Stanton & Todd, 1976) dealt with drug addicts or abusers. This is unfortunate, as the approach has shown enough promise with other types of disorders for Gurman and Kniskern to note that in every study in which it has been compared with other kinds of treatment it has emerged with equal or, in two-thirds of the studies, superior results. These authors also note that the most impressive findings have been obtained with "structural" family therapy (Minuchin, 1974; Rosman, et al., 1976), which is the kind being investigated in the present project.

The structural approach to family treatment has its underpinnings in the work of Minuchin (1974) and Haley (1976), and is an active technique in which the therapist attempts to bring about change in family interactions within the actual session. Specific tasks and concrete behavioral indicators are used. It is goal-oriented and symptom-focused and has been shown to be effective with different types of problems and different types of therapists.

It is our thesis that family patterns and family development are crucial in understanding and coping with this phenomenon. In examining current family process we are also assuming that present day events help to maintain the addiction of one or more members. We have undertaken a program designed to induce subjects to participate in an experience which strikes directly at family involvement and its current contribution to drug abuse in one or more of its members. Such a plan permits clarification of issues and resolution of problems and family patterns which, left alone, would perpetuate themselves. A further advantage of our family therapy approach is therapeutic contact with other family members who either are high risks themselves for the development of drug dependence and/or other symptomatology, or who tend to engender such patterns in other family members, particularly their offspring.

METHOD

Subjects

The sample consisted of 95 male addicts under age 36 (mean=26) plus their families of origin. All were enrolled in the Drug Dependence Treatment Center (DDTC) program of the Philadelphia VA Hospital. Half of the group was black and half white. They lived within one hour's drive from the research site. The index subjects had had military experience; thirty-five percent had been to Vietnam, 23 percent were married, and 54 percent lived with a parent. To be selected the index subjects must have been in contact with one of their parents or parent substitutes (e.g. stepmother, mother's boyfriend) at least weekly and the other at least monthly; these

"parents" had to be living together. Those who had previously been treated in family therapy were excluded. The addicts could not have had a history of psychosis, nor could they have had a VA medical disability of 30 percent or more. In addition, the drug-patient subjects had to have been (a) addicted to opiates for at least two years, (b) on methadone (at least initially), and (c) not have a sibling enrolled in the VA drug program.

VA Treatment Program and Intake Procedures

Family treatment was adjunct to the overall VA DDTC treatment program in which the patients were enrolled. For a given patient, the program included individual counseling, methadone, at least weekly urinalysis and detoxification. These VA patients were on some level of methadone maintenance, although abstinence from methadone was a desired goal of DDTC treatment.

All veterans who appeared for treatment at the DDTC were administered an intake interview to determine their eligibility for this project. They were seen by an intake counselor and psychiatrist. Approximately one-fourth were eligible for our study. The major reasons for exclusion were age, deceased parent, infrequent parent contact or nonaddiction to heroin. If judged eligible they were asked for additional information about their drug use, job history, family demographics, etc. Our project was then contacted to see if any treatment openings existed. If not, nothing was said to these patients about family treatment and they became part of our "non-family treatment" group. If an opening did exist they were assigned randomly to the available therapists.

It was the therapist's job to explain to the patient that family treatment would be part of his program. The patient had the option of refusing after the therapist had tried to enlist him. The therapist had two responsibilities at this point: one was to oversee the patient's drug treatment plan such as adjusting methadone dosage, etc., and the other was to get the family in. His goal was to have both parents and any siblings over age 12 living nearby come in with the patient for a family evaluation session (FES). The therapist did not know to which treatment conditions the family would be assigned. Families were randomly assigned to the three family treatment conditions - paid family therapy, unpaid family therapy, or family movie treatment. Treatment proceeded from that point.

Treatment Groups

Four treatment groups were involved, three of which included the families of the addicts during treatment. The fourth included family members only for the followup interviews. The treatment period (intake to termination) for family groups averaged 4 1/2 to 5 months in length.

Nine therapists were involved and they had at least two years experience, got weekly supervision and also served as drug counselors. In 86 percent of the cases they were matched by race with the

patients (black patient, black therapist, etc.).

1. Paid family therapy (N=18). At the end of the FES a contract was made with the family to attend 10 family therapy sessions. The usual rationale given was that the family is important for helping the addict get off and stay off of drugs. Sessions usually included most or all of the family. In some cases therapy extended beyond 10 sessions, particularly if a crisis occurred near termination.

This therapy mode also included reimbursement to counteract the low motivation for treatment which these families have historically shown. In brief, every family member over age 12 received $5 at each session he attended. He also got a chance to increase his payment, however, if the addict member had been "clean" that week, by means of a drawing following each session. For every family member present $5 was added to the sum to be drawn for, so that the total was as high as, say $30 if six members attended. If it was a "dirty" week the sum was held until the next week and the combined total for both weeks was drawn for at that time. Neither the standard payment nor drawing were provided for more than ten sessions. It also mobilized all family members to put pressure on each other to attend and on the addict to attend and abstain from drug use. Further, the use of clean urines as a contingency for reimbursement served as a check against the misuse of payment sums by the addict.

2. Unpaid family therapy (N=19). Procedures for this group were identical to those for the paid group except that no money (aside from the evaluation sessions) was provided to the family. This group allows determination of whether reimbursement is important in (a) getting people into treatment, (b) keeping them in, and (c) producing improvement.

3. Family movie treatment (N=15). This program required the family to come in once a week for 10 weeks to view 10 anthropology movies about people in various foreign cultures. The rationale was that "we find that families which at times have difficulties can be helped by seeing how people in other cultures and societies live and work together, i.e., it gives them a perspective." Movies were selected because, in contrast to family therapy, they did not permit much interaction among family members during their time at the research site. A research associate administered the movies and instead of having a family therapist the addicts in this group became patients of the VA DDTC Senior Drug Counselor. These families were paid and got urinalysis reports in the same manner as the paid family therapy group. Thus the movie program served as a control for the effects of reimbursement and the effect on the family of meeting every week for an hour. The latter should not be underemphasized, for most of these families rarely got together for family activities.

4. Nonfamily (methadone only) treatment (N=43). These were addicts at the DDTC who met all of our criteria for inclusion in the study but were not selected for one of the family treatment groups. Instead they underwent the usual DDTC treatment procedures and entered

the methadone, individual counseling and other programs; they were assigned a drug counselor. However, to be included in our study they had to remain in the methadone program for at least one month. In comparison with family treatment patients, this group provides us with a baseline estimate as to the treatment outcomes which can be expected with similar subjects in an ongoing multi-modal methadone program.

Followups

Followup interviews were obtained on patients in all four groups by two interviewers who had no involvement in the treatment. Some interviews were held in the clinic, while others included home visits. Race of interviewer and family were matched.

The period assessed stretched from the end of family treatment (approximately 18 weeks from intake date) to a point six months post-treatment. For the nonfamily group a parallel timespan was assessed.

Followup data usually included interviews with the addicts, and at least one or both parents, often supplemented by interviews with spouses, siblings, relatives, parole officer and drug counselor or therapist. All interviews with addicts were accompanied by urine samples taken and observed at the time. The 40 and 90 minute structured interview covered drug and alcohol use by addict and other members, employment or school progress of addict, living arrangements, family contacts of addict, medical problems, legal problems, and any other changes during the past six months.

The generic outcome measure employed is the percentage of days that a patient did not use a particular drug (or drugs) over the six-month period. Estimates were derived from the following sources: addict self-reports, family member or spouse reports, drug counselor and therapist reports, DDTC records/charts and urinalysis results. Employment and enrollment in school were also assessed.

The eight dependent or outcome variables measured were:

1. Percent days free of:

a. Heroin, opiates and illegal methadone
b. Legal methadone
c. All legal and illegal opiates
d. All nonopiate illegal drugs
e. All illegal drugs
f. Alcohol
g. All illegal drugs and alcohol

2. Percent "working" days spent working or in school.

The eight outcome variables, compared across all four groups, are presented in Table 1. Oneway analyses of variance were performed for all of them. Paid family therapy emerged as the most effective treatment across all drug variables. No difference emerged on the "working/school days" variable.

DISCUSSION

The efficacy of brief, paid family therapy for reducing opiate use seems to be established. Unpaid family therapy also appeared

ANALYSIS OF VARIANCE OF OUTCOME OVER SIX MONTHS POST TREATMENT

Dependent Variable	Non-Family Treatment (methadone) N=43	Family Treatment (N=52) Movie N=15	Unpaid Family N=19	Paid Family N=18	Level of Significance
Mean % days free of heroin, opiates & all illegal methadone	54.1%	82.6%	83.0%	85.5%	$p < .05$*
Mean % days free of legal methadone	41.8	27.1	45.0	61.9	NS
Mean % days free of all legal & illegal opiates	23.5	21.9	37.4	55.7	$p < .05$
Mean % days free of all non-opiate illegal drugs#	44.1	55.7	63.6	78.8	$p < .01$
Mean % days free of all illegal drugs	25.1	45.7	50.5	67.1	$p < .001$
Mean % days free of alcohol##	42.2	65.6	56.8	67.4	$p < .10$
Mean % days free of all illegal drugs & alcohol	10.1	25.0	27.2	43.1	$p < .05$**
Mean % "Working" days spent working or in school#	38.3	57.8	48.5	46.4	NS

Due to missing data, the N's for Non-family treatment for these variables were 39.

Due to missing data, the N for Non-family treatment for this variable was 38.

* For analysis, a logarithmic transformation was applied due to heterogeneity of variance: $x^1 = \log [(181-x) +1]$..

** For analysis , a logarithmic transformation was applied due to heterogeneity of variance: $x^1 = \log (x+1)$.

slightly more effective than movie treatment and nonfamily (methadone) treatment.

Reimbursement may have affected outcome, but its major impact was on attendance: the average number of sessions for paid family therapy was 9.3, for (paid) movie, 8.8, and for unpaid family therapy, 6.2 ($p < .005$). Payment seemed instrumental in getting families to participate. Of course it also mobilized them to focus on and support the addict's abstinence, since the family lost money if he was "dirty" and stood to gain if he was "clean."

One area for further study pertains to patients who refused to become involved in family treatment. This happened in 27 cases, 29 percent of those approached. We made comparisons across 18 demographic variables (age, level of addiction, employment, SES, etc.) between these refusers and the cases which became engaged. They differed significantly on two of these - a higher percentage of refusers were black and more of them were enrolled in school or training programs. We plan to obtain followup data on refusers to deter-

mine whether their outcomes were better or worse than engagers.

In sum, brief structural family therapy shows considerable promise as a way of conceptualizing treatment strategy and bringing about change in this patient group. It is rare that any kind of treatment can show the kind of improvement demonstrated here with any subset of heroin addicts. Whether the effects hold for a period longer than six months is a question left to longterm followup investigations which we are presently conducting.

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General Cardiovascular Pharmacology of l-α-Acetylmethadol (LAAM)

Stickney, J. L.; Eikenburg, D. C.; Keedy, J. D.

INTRODUCTION

LAAM, l-α-acetylmethadol, is an orally effective narcotic agonist with a duration of action that ranges from 48 to 72 hours (Fraser and Isbell, 1951, 1952). Jaffe and his coworkers were among the first to recognize the possible usefulness of LAAM in the medical treatment of persons physically dependent on heroin or related drugs (Jaffe et al., 1970; Jaffe and Senay, 1971). LAAM is now in the final stages of Phase III clinical testing (Whysner, 1976).

Initial cardiac studies showed that the drug, as well as its major metabolites (N-LAAM, l-α-acetylnormethadol and DN-LAAM, l-α-acetyldinormethadol; Billings et al., 1974) possess chronotropic (Stickney, 1977a) and inotropic (Stickney, 1977b) activity in isolated guinea pig atria. Subsequent studies have been concerned with the identification of mechanisms underlying these effects (Stickney, 1978a,b). Additional work has shown that the responses occur not only in cardiac tissues isolated from other species (Stickney and Keedy, 1978), but in vivo as well. We have observed cardiovascular responses to LAAM and congeners in anesthetized dogs and cats (Eikenburg and Stickney, 1978). Cardiac responses to LAAM have also been identified in unanesthetized dogs (Waters et al., 1978) and unanesthetized rhesus monkeys (Masten et al., 1978).

METHODS AND MATERIALS

Experiments on Isolated Tissue

The cardiac effects of LAAM and congeners were studied on tissues isolated from four species: guinea pig, rat, rabbit, and cat. The methods have been described in detail elsewhere (Stickney, 1977a,b).

Experiments In Vivo

Mongrel dogs or cats were anesthetized with pentobarbital sodium

administered intravenously (dogs, 30 mg/kg; cats, 35 mg/kg) and artificially respired with room air via a tracheal cannula. A femoral artery was cannulated and arterial blood pressure (BP) monitored via a Statham pressure transducer. The Lead II electrocardiogram (ECG) also was recorded. Heart rate (HR) was monitored using a tachograph.

Either analysis of variance or Student's t-test was used to determine significant differences between groups. The level of significance chosen was $p < .05$.

l-α-Acetylmethadol, l-α-acetylnormethadol and l-α-acetyldinormethadol (all HCl salts) were supplied by the National Institute for Drug Abuse (NIDA) from Research Triangle Park, North Carolina.

RESULTS

Experiments on Isolated Tissues

The inotropic and chronotropic effects of LAAM are summarized in Tables 1 and 2, respectively.

Experiments In Vivo

The intravenous administration of LAAM to anesthetized dogs significantly decreased HR, CF, and BP. The data are summarized in Table 3. N-LAAM and DN-LAAM effected similar responses. N-LAAM was more potent than LAAM and DN-LAAM.

Three parameters were monitored during a one minute occlusion of the common carotid arteries bilaterally: mean arterial blood pressure, heart rate, and myocardial contractile force. The three narcotic agonists significantly decreased the responses of all parameters. N-LAAM was most potent.

Table 4 shows that LAAM produced a significant dose-dependent decrease in HR and mean BP in cats. Myocardial contractile force was not monitored.

DISCUSSION

There are brief statements in both the clinical (Ling et al., 1976) and animal (Archer, 1976; Wolven and Archer, 1976) literature which suggest that LAAM may have cardiovascular effects. However, it appears as though these effects had not been studied in a systematic manner until the experiments in this laboratory were undertaken.

The data collated in this paper suggest that an investigation of the cardiovascular effects of LAAM in man is warranted. LAAM produced significant cardiac or cardiovascular responses in all four species examined.

Chronotropic activity was studied in right atria from three spe-

TABLE 1

Effect[a] of 1-α-Acetylmethadol on Contractile Force of Cardiac Tissue From Four Species

	1×10^{-8}[b]	1×10^{-7}	1×10^{-6}	5×10^{-6}	1×10^{-5}	5×10^{-5}	1×10^{-4}
Rat[c]	0	0.03±1.9	1.00±1.8	5.5±1.6	8.9±2.0	8.5±2.8	-14.6±5.1
Guinea pig[c]	8.08±1.1	11.88±2.5	10.6±3.7	16.13±4.9	19.3±3.1	3.95±6.3	-20.48±2.7
Rabbit[c]	-0.24±0.9	0	1.26±1.4	6.08±0.8	11.96±1.8	-10.74±2.1	-52.50±9.3
Cat[d]	0.80±1.1	-1.68±4.8	-1.93±3.7	-9.63±5.3	-17.87±7.1	-41.30±7.8	-61.23±8.0

[a]Percent change from control height of contraction ± SEM; [b]molar concentration of 1-α-acetylmethadol; [c]left atria; [d]right papillary muscles.

TABLE 2

Effect[a] of 1-α-Acetylmethadol on the Spontaneous Rate of Beating of Right Atria From Three Species

	1×10^{-8}[b]	1×10^{-7}	1×10^{-6}	5×10^{-6}	1×10^{-5}	5×10^{-5}	1×10^{-4}
Rat	-0.82±0.5	-0.83±0.5	-1.65±0.8	-0.85±1.0	0.27±1.6	-2.32±3.1	-11.22±4.4
Rabbit	0	0	-0.86±0.9	-9.02±0.2	-13.52±2.1	-20.12±4.9	-32.80±6.7
Guinea Pig	-1.47±0.7	-1.74±1.2	-6.03±1.42	-7.85±3.2	-22.7±7.9	-39.6±10.1	-71.3±10.6

[a]Percent change from control rate of beating ± SEM. [b]Molar concentration of 1-α-acetylmethadol.

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TABLE 3

Effect of 1-α-Acetylmethadol on Mean Arterial Pressure (MAP), Heart Rate (HR) and Myocardial Contractile Force (CF) in the Dog

	Control	0.027[a]	0.27	1.37	2.73	5.46
HR[b]	171.4 ± 7.1	170.8 ± 8.5	164.4 ± 8.2	121.6 ± 12.4	96.0 ± 10.2	93.4 ± 9.5
MAP[c]	132.2 ± 2.9	138.4 ± 10.0	125.0 ± 4.0	108.0 ± 4.3	103.2 ± 4.2	94.6 ± 6.1
CF[d]	70.0 ± 9.6	66.2 ± 8.3	64.5 ± 8.9	53.2 ± 8.2	49.5 ± 7.3	47.8 ± 7.6

[a]Dose of 1-α-acetylmethadol in mg/kg; [b]beats per min. ± SEM; [c]mm Hg ± SEM; [d]grams of tension ± SEM.

TABLE 4

Effect of 1-α-Acetylmethadol on Mean Arterial Pressure (MAP) and Heart Rate (HR) in The Cat

	Control	0.027[a]	0.27	1.37	2.73	5.46
HR[b]	193.0 ± 9.4	192.0 ± 8.8	192.0 ± 11.9	166.0 ± 6.6	128.0 ± 6.6	113.0 ± 5.4
MAP[c]	114.0 ± 5.6	116.8 ± 6.3	115.6 ± 6.1	105.4 ± 5.0	89.8 ± 4.3	79.0 ± 5.1

[a]Dose of 1-α-acetylmethadol in mg/kg; [b]beats per min. ± SEM; [c]mm Hg ± SEM.

cies. LAAM and congeners decreased the spontaneous rate of beating in all preparations. The results suggest that a general negative chronotropic action is an inherent property of the drug. Experiments carried out on anesthetized cats and dogs support this hypothesis. The narcotic agonists produced a dose-dependent decrease in heart rate in vivo. The in vivo studies have been extended and it appears that there are at least two mechanisms for the negative chronotropic response. One mechanism seems to be direct and similar to that found in the isolated preparations; the other appears to involve an interaction with the sympathetic nervous system (Eikenburg and Stickney, 1978).

A negative inotropic response was observed in isolated tissue preparations of four species. The mechanism by which LAAM produces the negative inotropic response has not been identified. An alteration in the disposition of Ca^{++} may play a role in the response (Stickney, 1978b). A negative inotropic response also was effected in the anesthetized dog.

LAAM was found not only to produce a significant depressor response in anesthetized dogs, but the drug also attenuated the pressor response to a one minute occlusion of the common carotid arteries bilaterally. These findings suggest that the drug has the potential for interfering with reflexes which normally act to maintain cardiovascular homeostasis.

The data obtained in these series of experiments indicate that cardiovascular effects of LAAM would be of toxicological rather than therapeutic significance because the concentrations of LAAM required to produce the effects are higher than those reported under conditions where drug administration to humans has been monitored carefully (Kaiko and Inturrisi, 1975; Lau and Henderson, 1975). However, such concentrations might be found under certain conditions: in persons who receive standard dose regimen but who metabolize the drug more slowly (Billings et al., 1974); in persons who accidentally or intentionally ingest excessive amounts of the drug. Finally, one cannot exclude the possibility that persons with chronic heart failure or other types of cardiovascular pathophysiology, and persons taking other medications which depress the heart might be sensitive to the cardiovascular effects of LAAM and congeners. In this regard, it is noteworthy that N-LAAM appears to be a more potent cardiovascular depressant than LAAM; the former has a longer biological half-life than the latter.

In summary, studies carried out in this laboratory and other laboratories (Lee and Berkowitz, 1977; Masten et al., 1978; and Waters et al., 1978) have yielded results which suggest that the cardiovascular effects of LAAM in man should be studied.

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On the Relative Efficacy of LAAM and Methadone

Whysner, J. A.; Thomas, D. B.; Ling, W.; Charuvastra, C.

INTRODUCTION

Prior to the VA-SAODAP Cooperative study, several clinical investigations had demonstrated that LAAM could be a safe and effective alternative to methadone for the maintenance of opiate addicts. Additionally, LAAM was a longer-acting drug, and so offered several advantages inherent in three-times-per week dosing: (1) lowered clinic costs, (2) an end to the problem of diversion, with its associated mortality, which resulted from methadone take-home doses, and (3) a less specific advantage, an opportunity to reorient patients from daily hassles and anxieties over drugs and dosages, to more socially acceptable concerns and pursuits.

The VA-SAODAP study, then, was designed to compare LAAM and methadone in a fully randomized double-blind fashion. The sample population was comprised of 430 street addicts from 12 VA hospitals. The duration of study treatment was 40 weeks. Intake began April 1973, and the last patient completed the study on March 31, 1975.

The study design specifically addressed two issues: (1) the relative safety and efficacy of LAAM, as compared with methadone, and (2) the safety and efficacy of two dose levels of methadone. Some investigators, such as Dole and Nyswander (1) had argued for relatively high doses of methadone (100 mg), whereas others, such as Goldstein (2) had determined that 50 mg was just as potent in providing an effective "blockade" against the effect of heroin.

This paper reports on the efficacy of three treatment regimens, LAAM, 80 mg TIW, and methadone, 50 or 100 mg daily, as assessed by random screens for urine opiates and symptoms and signs of chronic abstinence, in addition to several contingent variables, such as amount of criminal involvement.

The safety data for LAAM and for methadone have already been an-

alyzed in detail in previous publications (3) and will not be discussed here.

METHOD

Patients--Each of 12 VA hospital clinics contributed patients to the cooperative study; all clinics followed a common protocol. Patients were eligible for participation if they (1) met all the FDA criteria for admission to maintenance programs, (2) were men, aged 18-60, and (3) were not currently enrolled in another methadone program. Incapacitating or life-threatening conditions, disease requiring regular, repeated medication, psychotic states, epilepsy, and current severe alcoholism were also criteria for exclusion.

Drug treatment--Patients were randomly assigned, double-blind to one of three treatment groups, according to a schedule supplied centrally:

1. Methadone, stabilized at 50 mg daily
2. Methadone, stabilized at 100 mg daily
3. LAAM, stabilized at 80 mg TIW

For each patient, a series of individual-dose bottles, numbered from 1 to 280, was supplied. In all three groups, the initial dose was 30 mg; this was incremented by 10 mg each succeeding Monday, until the patient had achieved his stipulated target dose. The sequence of these increments was controlled by bottle number. The first 8 weeks of the study was considered as an induction period.

The two methadone groups were given active medication daily, but the LAAM group received active medication on Monday, Wednesday, and Friday only; placebo (dextromethorphan plus quinine) was given on the other 4 days.

Measures of efficacy--While the ultimate aim of any maintenance treatment is amelioration in the actual day-to-day lives of addicts, the primary pharmacological goal of any maintenance therapy must be the blockade of craving for illicit opiates. Therefore, in this study, the most direct, and objective, measure of treatment efficacy was considered to be the amount of decrease (or cessation) in the use of the primary drug of dependence.

The presence (or absence) of abstinence signs and symptoms, as noted on the Symptom-Sign Checklist (a prepared form comprised of 31 symptom-signs; complaints were elicited by general questioning), was also considered a direct measure of drug treatment efficacy. Indicators for this criterion included monthly vital sign readings (pulse, blood pressure, temperature: objective indicators), plus routine self-reports of symptom-signs and any information gained from drug-related early terminations from treatment (subjective indicators).

Patients also made periodic reports on their own opiate use, and,

at the end of the study or early termination, evaluated their treatment outcome, in terms of factors like criminal activity. Staff, as well, assessed the amount of illicit drug use by patients, and noted the degree of change in socioeconomic adjustment and social relationships.

Methods for testing urines--At the clinics, urine specimens were collected once per week on a random, unannounced basis, under direct observation to prevent substitution. Urine specimens were then screened for morphine by the Enzyme Multiplied Immunoassay technique (EMIT) and thin-layer chromatography (TLC). If both results were positive, the test was considered "confirmed"; if the EMIT was positive and the TLC was negative, the sample was hydrolyzed, and TLC was run again. If the second TLC procedure gave positive findings, the sample was considered positive.

RESULTS

Illicit opiate use--As shown in Table 1, patient urine data were categorized according to two criteria, "cohort" and "period". Two cohorts of patients were designated: those who had completed a minimum of 24 weeks in the study, and those who finished the scheduled 40 weeks. "Period" indicates which portion of the study is being considered: the first 8 weeks, or induction period, the entire study (0-40 weeks), including the induction period (irrespective of when individual patients terminated), or the study period between the end of the induction period and termination from the study (9-40 weeks). In terms of trends and patterns of illicit opiate use, this last period was considered the most significant.

If all clients with 4 or more urines collected are considered, the M-50 group shows a higher proportion of illicit opiate use than either the M-100 or the L-80 group. For the 24-week cohort, no differences were seen among groups during the induction period. But when the two later periods (9-40 and 0-40 weeks) are considered, significant differences emerge among the three treatment groups in terms of proportions of dirty urines. Now M-50 shows the highest proportion, followed by M-100; LAAM patients had the lowest proportion of illicit opiate use. Considering the 40-week cohort, the study completers, M-50 patients again show higher proportions of dirty urines, after the first 8 weeks of the study.

Thus, the trend that emerges from a consideration of these individual items shows an initial decline in dirty urines among all groups, but a gradual increase among the M-50 group, as the study proceeds. The M-100 group remains at a somewhat lower level, while the L-80 group shows a gradual decline across the study (this lower frequency of dirty urines among LAAM patients, after the first 8 weeks, was statistically significant). As demonstrated by the cohort analysis, these group differences resulted from changes in the behavior of individuals, rather than from differences in illicit drug use by those who terminated

within the drug groups.

The evaluation of patients' illicit drug abuse by clinic staff, as well as patients' self-reports on illicit opiate use, generally support these findings. The data indicate that the M-50 group has significantly higher levels of involvement with illicit opiate use.

An alternative approach to analysis of urine data, the Urine Index, was detailed in a previous publication (3).

Abstinence syndrome--The M-50 group showed a slight, but persistent, indication of abstinence, as evidenced by elevated blood pressure and temperature. For diastolic blood pressure change scores (comparing M-50 with M-100 and L-80) were statistically significant at weeks 12 and 28; systolic blood pressure change scores were significant at week 12. Considering change scores for temperature, M-50 was significantly different from M-100 and L-80 at weeks 4, 16, and 28. No evidence of abstinence was noted in either the M-100 or L-80 groups. Further, there was a slight excess of M-50 patients with multiple complaints related to underdosing.

Social adjustment--M-50 patients also did poorly in areas less directly related to the pharmacologic effects of the drug: they had significantly more criminal involvement (by self-report), higher proportions of arrests, and were more likely to spend time in jail.

DISCUSSION

In this study, LAAM patients not only showed lower levels of opiate use, but also a pattern of progressive improvement (after the initial 8-week stabilization period): a gradual decline in the proportion of dirty urines was observed over the course of the study. M-100 patients did less well, but, in general, tended to show decreases in illicit opiate usage over time that were similar to those in the L-80 group.

More striking were the results from the M-50 group: by every method of analysis used, this group showed both an excess of patients with high frequencies of dirty urines and a trend, over time, toward increases in numbers of positive urines.

A surprising finding in this study was a slight but statistically significant elevation in blood pressure and temperature. These measurements were taken at the time of dosing and appear to represent abstinence associated with the daily minimum in plasma concentration. The findings would suggest that M-50 are more likely to feel abstinence 24 hours after their last dose than do M-100 at 24 hours or L-80 patients at 48-72 hours.

Such findings suggest that the M-50 group experienced chronic

underdosing, during the study, and so attempted to compensate for such underdosing by reverting to their usual practice of using street heroin. The results from urine screens indicating underdosing (among M-50 patients) were corroborated by several other findings: the indications of abstinence and the poor outcomes on indices of social adjustment, as exemplified by the high proportion of arrests among this group.

The results of this large scale study, then, have established LAAM as a maintenance agent that demonstrates some superiority to methadone, in terms of ability to decrease the use of illicit opiates. Further, the conclusion of Garbutt and Goldstein that 50 mg of methadone is equally as effective for maintenance of addicts as higher doses, has been seriously challenged: patients given 50 mg of methadone daily showed consistently poorer outcomes, in several measures of efficacy, than either M-100 or L-80 subjects.

Some clinicians have felt that patients could be stabilized on any pre-established level of methadone, since they have presumed that the body is able to adjust its opiate needs to the level of maintenance agent prescribed. Our results suggest that such inflexibility may be unwise: individual patients should probably have methadone doses carefully tailored to meet individual needs.

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TABLE 1

ANALYSIS OF VARIANCE OF ILLICIT MORPHINE IN URINES WITH MEAN DEVIATIONS FOR SELECTED COHORTS AND TIME PERIODS

Cohort	Period	Mean Deviations M-50	M-100	L-80	P-Value	Other Significant Differences
All[a] Subjects	40 weeks	0.06	-0.03	-0.03	0.02*	e
24 Week[b]	1st 8 wks	0.00	0.01	-0.01	0.90	
24 Week	9-40 wks	0.08	-0.02	-0.08	0.00*	f
24 Week	40 wks	0.06	-0.01	-0.06	0.01*	f
40 Week[c]	1st 8 wks	-0.02	0.02	-0.01	0.79	
40 Week	9-40 wks	0.06	-0.01	-0.06	0.03*	f
40 Week	40 wks	0.05	-0.01	-0.05	0.12	
8 Week[d]	1st 8 wks	0.02	-0.01	-0.01	0.75	

*Categories in this column indicate significant ($p < .05$) differences between study medication groups as determined by the Parametric Test.

[a]All subjects who had at least 4 urines collected during the study are included in this analysis.
[b]All subjects who attended at least 24 weeks of the study are included in this analysis.
[c]All subjects who attended the entire 40 weeks of the study are included in this analysis.
[d]All subjects who attended at least the first 8 weeks of the study and had at least 4 urines collected are included in this analysis.
[e]Meth-50 significantly ($p < .05$) different from Meth-100 and LAAM-80.
[f]Meth-50, Meth-100, and LAAM-80 significantly different from each other.

Lack of Toxicity of High Dose Propoxyphene Napsylate When Used for Maintenance Treatment of Addiction

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Within the last six years clinical reports have suggested that propoxyphene can be used for detoxification and maintenance treatment of narcotic addicts (Tennant, 1974, 1975; Inaba, Gay, Whitehead, 1974). Propoxyphene is chemically similar to methadone and has weak narcotic agonist properties (Jasinski, Pevnick, Clark, 1977). Probably only addicts with low levels of physical dependence can be treated comfortably with propoxyphene as the doses necessary to suppress abstinence symptoms, even in this selected group, are high (800-1400 mg/day of napsylate salt; 500-900 mg/day of the hydrochloride). At these doses, side effects often occur (Tennant, 1973; Mattson, Weisman, Levy, 1969). Typically, they reflect central nervous system irritability or depression and include nausea, dysphoria, dizziness, drowsiness, tremulousness, anxiety and seizures. They can be minimized by giving propoxyphene in divided doses rather than in one single dose (Tennant, 1973).

A recently completed double blind study has shown that low dose (maximum 36 mg/day) methadone maintenance is superior to high dose (maximum 1200 mg/day propoxyphene napsylate for maintenance treatment (Woody, Mintz, Tennant, this volume). Another double blind study has shown that methadone (initial dosage of 24 mg/day) suppressed abstinence symptoms better than propoxyphene napsylate (800 mg/day) in a heroin detoxification program (Tennant, Russell, Casas, 1975). These findings are consistent with the early work of Fraser and Isbell (1960) and the more recent findings of Jasinski et al.(1977).

Though propoxyphene appears to be generally less effective than methadone in narcotic detoxification and maintenance, there may be some cases where propoxyphene may be preferable. Propoxyphene is less euphorogenic, less physically addicting, and is therefore less liable to be abused than methadone and other narcotics. It may appeal to individuals who have low levels of physical dependence and who need medication but wish to avoid stronger opiates; and it is stocked and easily available in most pharmacies.

However, propoxyphene is not approved by the Food and Drug Administration for use in the treatment of addiction. One reason for this lack of approval is that there are little data on possible toxic effects from the chronic use of high doses in humans. Kiplinger et al (1971) studied humans dosed with the hydrochloride (260 mg/day, n = 24) and napsylate (400 mg/day, n = 25) salts. These doses, which are within the usual analgesic range, were continued for six months and no changes in urine, blood, physical exams or electrocardiograms were found. Emerson et al.(1971) found weight loss and increases in alkaline phosphatase in dogs who were given three times the normal human dose of both the napsylate and hydrochloride salts, over a period of 90 days. Higher doses produced liver enlargement and fatty changes. They also found that rats given 40 to 100 times the human dose over 90 - 180 days developed enlarged and fatty livers.

This paper presents toxicologic data from two studies, one done in Philadelphia and one in Los Angeles, in which high doses of propoxyphene napsylate were compared with low doses of methadone for maintenance treatment of narcotic addicts. Protocols were almost identical in each study and the clinical results, mentioned earlier, are detailed in a separate paper (Woody, Mintz, Tennant, this volume).

In this study, addicts applying for maintenance treatment were randomly assigned to one of two groups: one received low dose methadone, the other high dose propoxyphene napsylate. Only patients who were non psychotic, who had no serious physical illnesses and who were judged (by history and physical exam) to have a low level of physical dependence were approached about participating in this study. Patients received medicines daily, seven days per week, for a maximum of 6 months. Details of the dispensing procedure have been outlined in another paper (Woody, Mintz, Tennant,this volume). After informed consent was obtained, patients were started on 12 to 24 mg of methadone per day or 400 to 800 mg of propoxyphene napsylate per day. They were observed closely during the next one to two weeks with an eye to dosage adjustment and side effects. Dose was gradually increased over two weeks to an average level of 32 mg/day of methadone or 500 mg twice daily of proxyphene napsylate. One hundred forty-seven subjects were treated in Philadelphia (Propoxyphene 79, Methadone 68) and 80 in Los Angeles (Propoxyphene 46, Methadone 34). A physical exam with CBC, SMA 6/12, and urinalysis was done at intake, at two weeks, four weeks and each month thereafter until termination. A chest x-ray and an EEG were done at intake and at six months, or termination. Patients who stayed on the study for the entire six months were usually switched to low dose methadone treatment, although a few detoxified.

RESULTS

Two types of analyses were performed on the monthly toxicologic data for subjects in the propoxyphene study groups. In the first

analysis the absolute values of the test results were examined at each monthly interval using a repeated measures analysis of variance design. This type of analysis was selected under the assumption that the accumulated effects of the medication might produce progressive changes in the test results over the monthly examination points. In the Philadelphia group, 79 patients began propoxyphene treatment; of those, 57 dropped out prior to one month and were not considered in the analyses. Three separate analyses were computed for those remaining subjects who received two months of treatment (n=22), those who received four months of treatment (n = 17), and those who completed six months of treatment (n = 14). Results of each of these analyses indicated no significant changes in the absolute values of the laboratory results in 27 of the 28 tests. Subjects who had completed six months of propoxyphene treatment showed a significant reduction in total bilirubin ($p < .05$) from a mean of .87 baseline, to a mean of .50 at the six month interval. This constituted a change from an abnormally high value to a level within normal limits.

In the Los Angeles group 46 patients were placed on propoxyphene, and 36 remained in treatment for a month. Analyses of the toxicologic data on these 36 subjects produced results which were comparable to the Philadelphia findings. That is, none of the tests analyzed showed evidence of a significant change over the course of the study.

While these analyses demonstrated no significant changes in the mean values of the laboratory tests, it was possible that there were changes in the incidence of abnormal values in these tests over the course of the study. To test this possibility the Philadelphia subjects were again divided into the three length of treatment groups, and chi square analyses were computed on each laboratory test using frequency of abnormal values as the measure. Again, twenty-six of the laboratory tests demonstrated no significant changes in the frequency of abnormal values over the course of the study. However, SGOT and total bilirubin analyses were both found to show significant decreases ($p < .05$) in the frequency of abnormal values for those subjects who completed six months of the study.

Analysis of the EKG data on the propoxyphene subjects from Philadelphia demonstrated that virtually all patients had values within normal limits. While two of the subjects had slightly abnormal results at baseline, each became normal during the study. EKGs were examined carefully by a cardiologist for signs of the development of conduction disturbances and none were found. EEGs showed signs of medication effects, similar to those seen with sedatives and minor tranquilizers. No seizure activity was noted at any time either clinically or on EEG. The physical complaints reported by the propoxyphene subjects during the study were generally typical of the assorted illnesses commonly seen in patients on a maintenance program. Nineteen of the propoxyphene subjects reported abnormal physical symptoms at some time during the study. The most common

abnormality reported was respiratory infection which occurred in four patients. In addition, a small percentage of these subjects reported increased anxiety, restlessness, and confusion which stopped when propoxyphene was discontinued.

To summarize, analyses of the toxicologic data and reports of physical complaints for those subjects maintained on high doses of propoxyphene showed no general evidence of systematic change in the absolute values of the tests or in the frequency of abnormal results over the course of the study. Two specific tests of liver function did show evidence of change, in the direction of normalization, for those subjects who completed six months of medication. It should be noted that these results were paralleled by the data for the methadone group who similarly showed no general evidence of change in toxicological tests, nor in reports of physical complaints over the course of the study.

Two rather serious incidents did develop during the course of propoxyphene treatment and require comment.

One propoxyphene patient, a 52-year-old male with mild diabetes, developed a transient cerebral ischemic attack. This required hospitalization and resolved within 24 hours. Over the next two years, no subsequent episodes occurred. A second patient became obtunded apparently as a result of propoxyphene and sedative drugs. He was receiving 300 mg propoxyphene twice daily and the incident occurred on the third treatment day. He was known to abuse alcohol, sedatives and benzodiazepines along with narcotics. When interviewed in a local hospital several days after the incident, he claimed to have taken two 30 mg flurazepam capsules and five "pills" of unknown content, in addition to the study medication. He may have taken more medication with the propoxyphene, but no additional history or toxicologic data were available.

DISCUSSION

One hundred twenty-seven patients received at least one dose of propoxyphene and the average daily dose used by patients who continued on this study was within the lower limits reported to be fatal in nontolerant humans who take this drug rapidly and at one time (Hudson, Barringer, McBay, 1977; Rejent, Michalek, Lehotay, 1977). Other than the single patient who became obtunded while taking unknown drugs and benzodiazepines with propoxyphene, we did not see any cases resembling the propoxyphene overdoses reported by others (McBay, Hudson, 1975; Sturner, Garriott, 1973; Carson, Carson, 1977). We think this reflects an absence of CNS depression by propoxyphene in this population, probably due to tolerance for narcotic agonist effects. Of course, this tolerance is absent in nonaddicts who take propoxyphene impulsively and often with suicidal intent (Hudson, Barringer, McBay, 1977).

The only consistent toxic effect observed was a syndrome which could be characterized as central nervous system "irritability." It usually consisted of increased anxiety, restlessness, or confusion,

which stopped when the drug was discontinued or when the dose was lowered. We noted these symptoms in 12% of patients who took propoxyphene for more than one month.

In conclusion, this study does not show clear evidence of serious toxicity when propoxyphene napsylate is used for maintenance treatment of addiction in divided doses, starting with a maximum of 400 mg twice daily and increasing by as much as 200 mg/day to a maximum of 600 mg twice daily. Propoxyphene does not appear to work as well as methadone for maintenance or detoxification (Woody, Mintz, Tennant, this volume), but clearly it works with some addict patients.

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MCV 4176
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NIH 8062
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NIH 8216
See 2-Methyl-5-phenyl-6,7-benzomorphan hydrobromide

NIH 8225
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NIH 8240
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NIH 8242
See 1-(beta-Carbethoxyethyl)-4-carbethoxy-4-phenylpiperidine hydrochloride

NIH 8251
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NIH 8299
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NIH 8310
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NIH 8366
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NIH 8377
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NIH 8400
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NIH 8636
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NIH 8684
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NIH 8687
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NIH 8714
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NIH 8715
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NIH 8859
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NIH 8877
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NIH 9230
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NIH 9261
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NIH 9365 B
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NIH 9369 A
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NIH 9468
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NIH 9484
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NIH 9506
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NIH 9509
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NIH 9512
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NIH 9513
See dl-trans-5,6,6a beta, 7,8,9,10,10a alpha-Octahydro-1-acetoxy-9 beta-hydroxy-6 beta-methyl-3-(5-phenyl-2-pentyloxy)-phenanthridine hydrochloride

NIH 9539
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NIH 9541
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NIH 9542
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NIH 9548
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NIH 9549
See 2-(2,6-Dichloro-anilino)-2-imidazoline hydrochloride

NIH 9551
See 10-m-Hydroxyphenyl-2-phenethyl-cis-decahydroisoquinoline

NIH 9559
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NIH 9560
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NIH 9561
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NIH 9562
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NIH 9563
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NIH 9564
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NIH 9584
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NIH 9607
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NIH 9612
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NIH 9613
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NIH 9614
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NIH 9624
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NIH 9625
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UM 485
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UM 604
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UM 610
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UM 729
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UM 998
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UM 1095
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